

National Institute of Allergy and Infectious Diseases

# PROFILE

Fiscal Year 2005



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES



NATIONAL INSTITUTES OF HEALTH



NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Front cover image: This is a representation of *Treponema pallidum*, the organism that causes syphilis.

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This is a stylized representation of an antibody, a protein made by the body's immune system cells to protect it against invading foreign substances.

## INTRODUCTION

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to understand, treat, and prevent infectious and immune-mediated diseases. For more than 50 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world.

This *Profile*, which is published annually, describes the Institute's activities in basic research and clinical investigation and provides overviews of the major accomplishments and goals of the various scientific programs within the Institute. The *Profile* also includes information about the organization and staff of NIAID; the Institute's budget; and its extramural grants, contracts, and research training programs. Most importantly, it conveys the Institute's twofold mandate. First, NIAID must plan and execute a comprehensive and long-term basic and clinical research program on well-recognized endemic infectious and immune-mediated diseases. Second, it must respond quickly with targeted research to meet new and unexpected infectious disease threats as they arise, often in the form of public health emergencies. In this latter respect, NIAID is unique among the institutes of the National Institutes of Health (NIH). The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as bioterrorism; emerging and re-emerging infectious diseases, including acquired immunodeficiency syndrome (AIDS), influenza, severe acute respiratory syndrome (SARS), West Nile virus, malaria, and tuberculosis; and the increase in asthma prevalence among children in this country.

Despite advances in medicine and public health such as antibiotics, vaccines, and improved sanitation, the World Health Organization estimates that infectious diseases still account for

approximately 26 percent of all deaths worldwide, including about two-thirds of all deaths among children younger than 5 years of age. The pathogens are not static, but change dramatically as new microbes emerge and familiar ones re-emerge with new characteristics or in unusual settings.

Influenza is a classic example of a re-emerging disease. Influenza viruses continually accumulate small changes such that a slightly different vaccine must be made for each influenza season. When a new influenza virus against which people have no natural immunity emerges, a worldwide pandemic can result if the virus is able to transmit efficiently from person to person. In 2005, the accelerated spread among domesticated chickens of a virulent strain of H5N1 avian influenza that spread in a limited fashion from chicken to human spurred national and international public health professionals to prepare for the possibility of a global pandemic. For such a situation to develop, the H5N1 strain would need to acquire the ability to spread efficiently from animal to human and from human to human. On November 1, 2005, President George W. Bush announced the *National Strategy for Pandemic Influenza*. The *HHS Pandemic Influenza Preparedness and Response Plan*, an integral component of the *National Strategy*, designates NIAID as the lead agency for scientific research and clinical trials to foster product development, particularly vaccines and antiviral drugs, to prepare our nation for a potential human influenza pandemic.

Our ability to cope with an influenza pandemic will depend to a large extent on how well we cope with seasonal influenza, which each year kills an average of about 36,000 people in the United States alone. The serious vaccine shortage resulting from a manufacturing plant contamination that occurred in the 2004–2005 influenza season underscored the difficulties in annually renewing the influenza vaccine supply and highlights the need to move toward adoption

of newer vaccine manufacturing techniques and other strategies that can improve the surge capacity, flexibility, and speed with which vaccines are made. NIAID supports numerous research projects that lay the foundation for improved influenza vaccine manufacturing methods, new categories of vaccines that work against multiple influenza strains, and the next generation of anti-influenza drugs. NIAID also conducts surveillance for the molecular evolution of influenza viruses among animals and humans in Asia and elsewhere, and tracks changes in influenza viruses that might allow them to be transmitted more easily among people.

NIAID also focuses on other emerging and re-emerging infectious disease threats around the world. Malaria is a substantial and growing problem compounded by the emergence of drug-resistant malaria parasites and insecticide-resistant mosquito vectors. NIAID supports a large malaria research portfolio. One recent study in mice identified a specific parasite gene that is essential for full maturation of the parasites, a finding that could be useful in developing an effective malaria vaccine. NIAID also supports a large portfolio of research to develop new drugs, vaccines, and diagnostics for tuberculosis (TB), which is estimated to affect one-third of the world's population and is especially common among persons infected with HIV. Two novel, genetically engineered TB vaccines developed with NIAID support recently entered phase I clinical trials in the United States. These promising candidates are the first new TB vaccines to be tested in more than 60 years.

Vaccine research supported by NIAID has led to new or improved vaccines for a variety of serious diseases, including rabies, meningitis, whooping cough, hepatitis A and B, chickenpox, and pneumococcal pneumonia. With our partners in academia and industry, NIAID works to develop new vaccine candidates to prevent diseases for which no vaccines currently exist, improve the safety and efficacy of existing vaccines, and design

novel vaccine approaches based on new vectors and adjuvants.

Despite recent progress in treatment and prevention, human immunodeficiency virus (HIV) disease and AIDS continue to exact an enormous toll throughout the world. An estimated 40 million people worldwide are living with HIV/AIDS, and their number is increasing by more than 5 million people every year—about 14,000 each day. More than 25 million people with HIV have died of HIV-related disease since the pandemic began.

To advance understanding, treatment, and prevention of HIV/AIDS, NIAID has established research collaborations with colleagues in more than 50 countries to develop comprehensive approaches to the HIV pandemic. These collaborations already have yielded important results, most notably in developing methods to reduce mother-to-child transmission of HIV. Development of a vaccine that protects against HIV/AIDS is one of the highest priorities of NIAID. To help overcome the extraordinary scientific challenges of HIV vaccine development, NIAID established the Center for HIV/AIDS Vaccine Immunology (CHAVI) in June 2005. CHAVI's mission is to tackle the fundamental immunological obstacles in HIV vaccine research and to design, develop, and test novel HIV vaccine candidates.

NIAID-supported researchers have made critical discoveries concerning the basic biology of HIV and the immune response to HIV infection, which in turn have led to the development of therapies that suppress the replication of the virus in the body. The use of potent combinations of anti-HIV drugs, many of which were developed with NIAID support, has dramatically reduced the numbers of AIDS deaths in industrialized countries and has saved the lives of hundreds of thousands of people in developing countries in sub-Saharan Africa, the Caribbean, South America, and Asia. Although much has been

learned in recent years, NIAID continues to investigate how the virus destroys the body's immune system and why the body fails to contain and eliminate the virus, both of which are critical for identifying additional targets for therapeutic interventions and vaccines.

The potential use of biological agents in a terrorist attack is a serious threat to the citizens of our nation and the world. Research to develop countermeasures against this threat is a key focus of NIAID. The *NIAID Strategic Plan for Biodefense Research*, developed shortly after the terrorist attacks of 2001, outlines three essential pillars of the NIAID biodefense research program: *infrastructure* needed to safely conduct research on dangerous pathogens; *basic research* on microbes and host immune defenses, which serves as the foundation for applied research; and targeted, milestone-driven development of *medical countermeasures* to create the vaccines, therapeutics, and diagnostics that would be needed in the event of a bioterror attack. In fiscal year (FY) 2003, NIAID was assigned the role of coordinating and facilitating NIH research into countermeasures to mitigate harm to civilians from chemical and radiological/nuclear weapons.

Two National Biocontainment Research Facilities as well as 13 Regional Biocontainment Laboratories, in which scientists will be able to safely contain and study dangerous pathogens, are now planned or under construction. NIAID also has established a nationwide network of 10 Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases research. The investment in biodefense research already has yielded substantial dividends. NIAID basic research and clinical trials are greatly increasing our ability to respond to the threats of smallpox, anthrax, and Ebola with new and improved vaccines, and this work promises to yield new insights relevant to both common and newly emerging infectious diseases that afflict people in the United States and abroad. In particular, the advancement of knowledge

about infectious organisms that could be used as weapons should also have an enormous positive impact on the ability to diagnose, treat, and prevent established major infectious diseases, such as malaria, tuberculosis, and HIV/AIDS, as well as emerging and re-emerging infectious diseases such as West Nile virus, dengue, influenza, and multidrug-resistant microbes. For example, in FY 2005, NIAID-supported scientists discovered that it might be possible to halt a poxvirus infection by administering a cancer drug aimed not at the virus but at the host cellular machinery that the virus needs to spread from cell to cell.<sup>1</sup> This research suggests a means of circumventing antiviral drug resistance for other viruses.

Another important NIAID research focus is the immune system, the complex network of cells, tissues, and organs that work together to defend the body against attacks by foreign invaders such as bacteria, viruses, parasites, and fungi. When the immune system attacks the wrong target, however, many diseases can result, including asthma and allergic diseases, rheumatoid arthritis, and other illnesses that cause significant, chronic disability in the United States and throughout the world. NIAID-supported research in basic and clinical immunology has led to many promising approaches for treating individuals with immune-mediated conditions such as multiple sclerosis, type 1 diabetes, and asthma. For example, researchers are developing novel ways to selectively block inappropriate or destructive immune responses while leaving protective immune responses intact, an area of research known as tolerance induction. NIAID has established the Immune Tolerance Network, a comprehensive program in which international researchers pursue research in immune tolerance induction. Currently, NIAID supports more than 40 clinical trials of immune tolerance strategies to treat autoimmune diseases, allergic diseases, and transplant rejection.

NIAID-supported research in immune-mediated diseases led to other significant advances in

FY 2005, such as a novel way to noninvasively assess the risk of kidney graft rejection by using immunologic and genetic biomarkers present in urine. If validated in larger studies, use of these biomarkers would allow physicians a noninvasive way to monitor transplant recipients for signs of organ rejection and to intervene before organ injury occurs. This would represent a significant advance in the clinical management of transplant patients.

NIAID also remains committed to improving the health of children with asthma, particularly those who live in our nation's inner cities. NIAID-supported researchers published the results of a study on the cost-effectiveness of home-based interventions that reduce exposure to common allergens such as cockroaches, house dust mites, and tobacco smoke. The study indicated that such interventions can result in 24 percent fewer unscheduled clinic visits, and a 13 percent reduction in the use of albuterol inhalers, small applicators that deliver asthma medication directly into the lungs. The reduction in symptoms persisted for at least 1 year after the intervention was stopped, showing that tailored interventions may have a substantial long-term

impact on asthma symptoms and healthcare resource use among inner-city children. For example, unscheduled clinic visits were reduced by 24%. The reduction in symptoms persisted for at least one year after the intervention was stopped.<sup>2</sup>

Much remains to be discovered about many infectious and immune-mediated diseases and how best to diagnose, treat, and prevent them. However, with its strong array of basic, applied, and clinical studies, and talented investigators in the United States and abroad, NIAID will continue to develop innovative technologies and treatments to combat a wide range of important diseases that afflict humanity.



**Anthony S. Fauci, M.D.**

*Director*

*National Institute of Allergy and Infectious Diseases*

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<sup>1</sup> Reeves PM et al. Disabling poxvirus pathogenesis by inhibition of Abl-family tyrosine kinases. *Nature Med.* 11(7):731-739 (2005).

<sup>2</sup> M Kattan et al. Cost-effectiveness of a home-based environmental intervention for inner-city children with asthma. *Journal of Allergy and Clinical Immunology* DOI:10.1016/j.jaci.2005.07.032.

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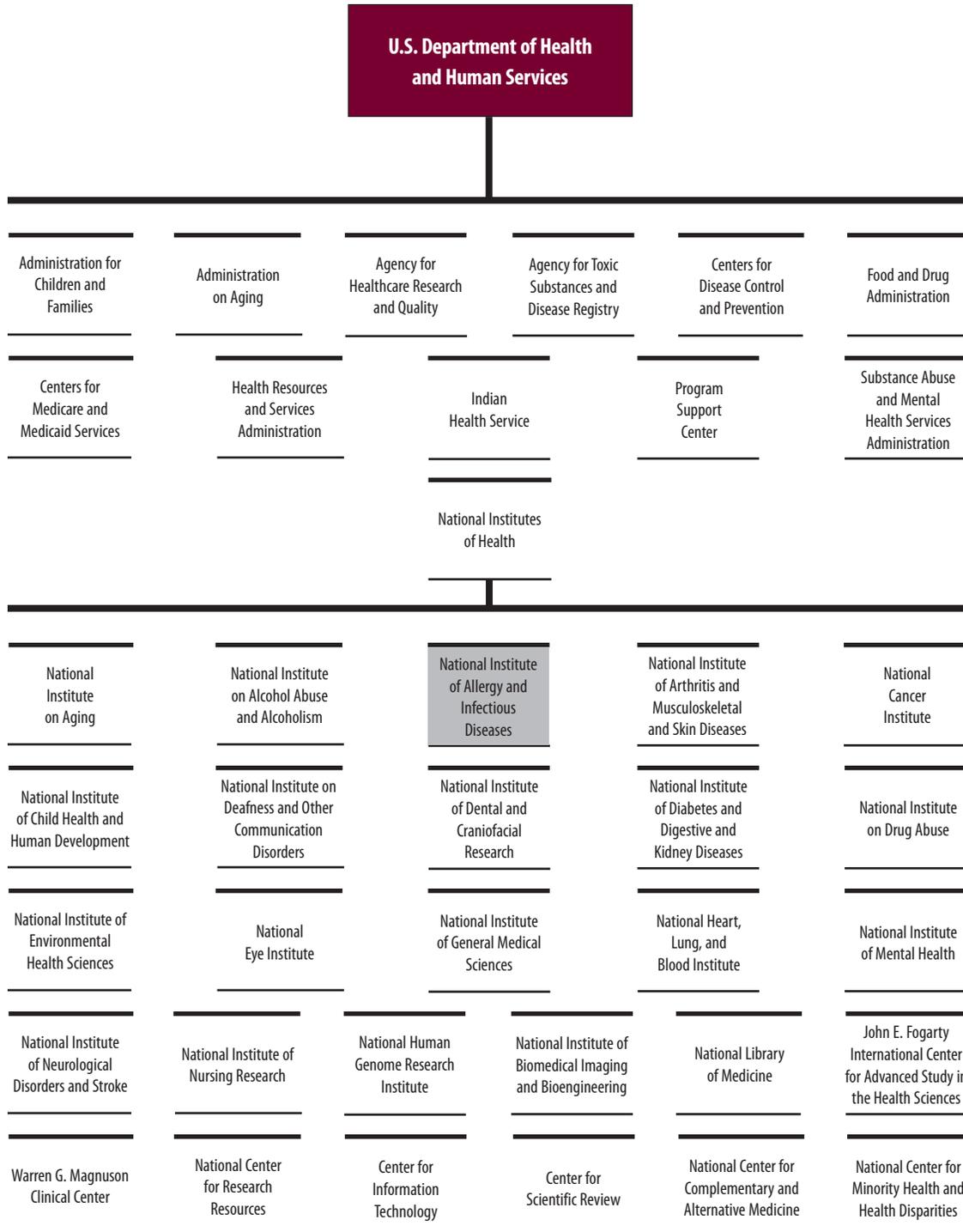
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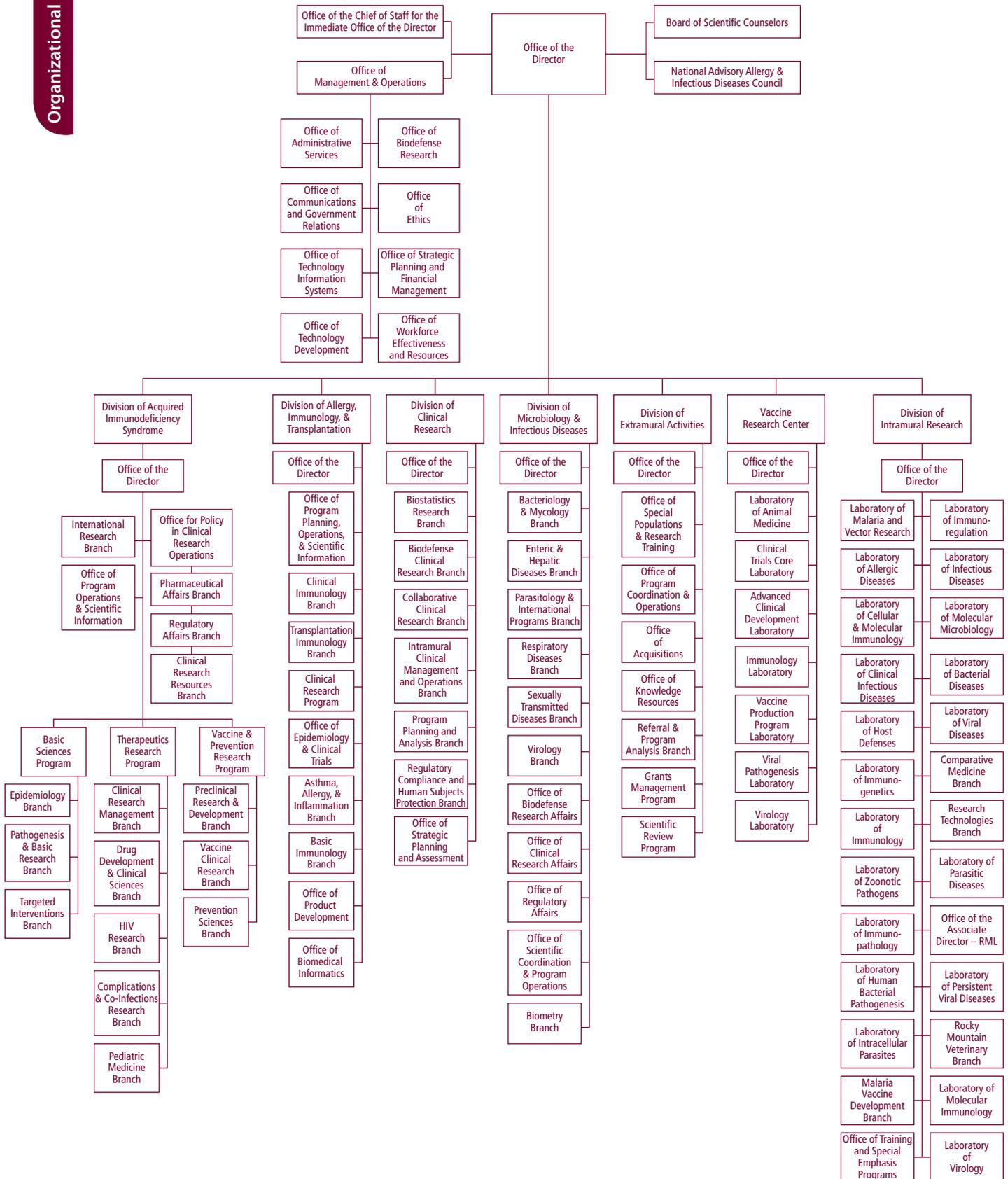
# ORGANIZATIONAL STRUCTURE



## LOCATION OF NIAID IN THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES



# NIAID ORGANIZATIONAL CHART



# ORGANIZATIONAL OVERVIEWS



## OFFICE OF THE DIRECTOR

During the past several years, the program responsibilities of NIAID have increased in scope and complexity, most notably in biodefense research, international presence, and preparations for the possibility of pandemic influenza. To address these changing needs and to improve the efficiency of the operations of the NIAID Office of the Director (OD), the Institute has significantly reorganized the OD offices. The new infrastructure and more strategically defined roles and responsibilities will maximize the ability of NIAID to achieve its mission to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. The process of reorganizing OD offices began in 2004; the new office structure took effect in April 2006. Additional changes will be announced as they become official.

The NIAID OD provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. OD is the chief liaison with the Director of NIH, other components of the Department of Health and Human Services (DHHS), other Federal agencies, Congress, professional societies, voluntary health organizations, and additional public groups. The activities of OD include advising and guiding the NIAID leadership on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs. Offices within OD provide critical management and administrative support to the Institute. By carrying out their individual tasks, OD offices play key roles in helping the Institute achieve its mission. Brief descriptions of OD offices follow.

The **Office of the Chief of Staff for the Immediate Office of the Director** manages and directs executive-level activities, functions, and priority-setting for all tasks occurring within

the Immediate Office of the Director (IOD), NIAID. IOD manages critical points of contact and related information flow to resolve and respond to external inquiries involving trans-NIAID and trans-NIH research issues. IOD addresses the political and cultural implications of current research and the initiation or expansion of research in specific areas by coordinating communications with outside lay, professional, and other organizations; brings the perspective of the NIAID Director to the development of NIAID program goals and objectives; advises and assists the Director, the Deputy Directors, and other key officials on all aspects of the mission, activities, and functions of the IOD; and is responsible for overseeing the effective and efficient planning and coordination of executive operations within the IOD.

The **Office of Management and Operations (OMO)** provides mission- and values-based business leadership, direction, support, and assistance to NIAID's national and international programs and activities. OMO oversees and directs the business management and administrative functions of the Institute, government relations and public communications, coordination of the Institute's global research effort, technology development, biodefense research, and policies and procedures for business and program management activities. OMO maintains liaison with and represents the Institute to NIH and DHHS officials and is responsible for the leadership and policy direction of overall program support and business management functions.

OMO directs and coordinates the activities of the following offices and operations:

- The **Office of Administrative Services (OAS)** directs, coordinates, and conducts specific administrative activities of the Institute. OAS advises the Director and senior staff on program management

and develops administrative policies and procedures.

OAS directs and coordinates the activities of the following branches and operations:

- The **Extramural Administrative Management Branch (EAMB)** advises the staff of the extramural programs on administrative policies and practices, and provides administrative support services to the extramural programs. EAMB analyzes the effects of changes in administrative policies and practices by organizational levels above NIAID, appraises the Deputy Director for Science Management of these effects, and helps coordinate the handling of administrative or management problems that cross program lines and cannot be resolved at the program level.
- The **Intramural Administrative Management Branch (IAMB)** coordinates the handling of all administrative, management, and facility support problems associated with the Division of Intramural Research (DIR). IAMB advises the staff of the DIR Director and other key officials about administrative policies and practices and provides overall administrative support services to DIR.
- The **Management Services Branch (MSB)** advises the NIAID Director and other senior staff on general management, administrative issues, and policies for the Institute. MSB develops, implements, and provides advice on regulations, policies, and procedures for the Institute; prepares staff papers and reports on general management issues; and analyzes the effects of changes in administrative policies and practices by organizational levels above NIAID. MSB provides general administrative and support services for OD, provides foreign travel processing services to OD, and designs and conducts management studies and surveys.
- The **Office of Biodefense Research (OBR)** plans, coordinates, implements, and supports the biodefense research efforts of NIAID, including critical research to develop medical countermeasures against biological, radiological/nuclear, and chemical threats. OBR also executes the Trans-NIH Intramural Biodefense Research Program, and coordinates biodefense and biodefense-related research issues across NIH through committees such as the NIH Biodefense Research Coordinating Committee. OBR disseminates information on the Institute's biodefense research programs, policies, and funding opportunities, and interacts with DHHS and other Federal agencies on many biodefense and security issues.
- The **Office of Communications and Government Relations (OCGR)** oversees efforts to interpret and disseminate the goals and results of NIAID research programs and projects to all its constituents, including the biomedical community, Congress, the media, specialized groups, physicians and healthcare providers, other federal agencies, and the general public at national and international levels. OCGR develops the Institute's short- and long-term communications policies, goals, objectives, and strategies; serves as the liaison and point of contact for all legislative matters; coordinates responses to all NIAID-directed media inquiries; and writes news releases, Web content, and statements directed to the media. These include requests for information and records submitted under the Freedom of Information Act (FOIA) and Privacy Act (PA) programs. OCGR writes the content for many NIAID print publications and the NIAID Web site,

manages the Web site, and serves as the Institute's liaison with appropriate voluntary, advocacy, and professional societies.

OCCGR directs and coordinates the activities of the following offices and operations.

- The **Digital Policy and Information Office** oversees the Institute's Web policy, content, and standards.
- The **Freedom of Information Office** responds to requests for information submitted under the FOIA and PA programs.
- The **Office of Global Research (OGR)** provides coordination of NIAID's international activities through a matrix of international liaisons. OGR stimulates new initiatives in international research and assists in planning for international programs. Such programs include collaborative international research programs on selected infectious diseases of substantial health importance in developing countries, as well as NIAID intramural and extramural worldwide biomedical research on infectious and immunological diseases. OGR helps stimulate communication across the Institute on international matters, provides technical support to NIAID international research projects and staff assigned overseas, and functions as the liaison with the Fogarty International Center and other relevant international programs within NIH and with other Federal entities. OGR maintains comprehensive knowledge of and information for the NIAID international research portfolio.
- The **Legislative Affairs and Correspondence Management Branch (LACMB)** responds to congressional and public inquiries. LACMB prepares congressional briefings, testimony, and reports, analyzes legislation, and assists with correspondence and other requests for information from the NIH Executive Secretariat.
- The **News and Public Information Branch (NPIB)** coordinates responses to media calls and writes and disseminates news releases, Web pages, and other resources for the media. NPIB staff members also develop and disseminate pamphlets, fact sheets, and other public information materials; coordinate logistics for NIAID lectures, exhibits, and other special events; oversee the NPIB support contract; and coordinate public liaison and selected outreach activities.
- The **Office of Ethics (OE)** administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public. OE develops and recommends policies and procedures related to employee standards of conduct, financial interests and disclosure, and outside activities. OE reviews and approves financial disclosure reports and requests for outside activities, maintains all records associated with its ethics functions, and provides advice and assistance to employees regarding the application of the ethics laws, regulations, and policies. In addition, OE provides ethics training, serves as the NIAID liaison for ethics issues to the DHHS Office of the General Counsel and the Office of Government Ethics, and provides advice to OD.
- The **Office of Strategic Planning and Financial Management (OSPFM)** directs and coordinates the Institute's strategic planning and evaluation activities, integration of long-term financial and capital asset resource requirements, budgeting, financial management activities, and knowledge management. In collaboration with members

of the Institute's scientific Divisions and executive management, OSPFM develops, directs, and coordinates strategic plans, policies, goals, objectives, strategies, and techniques in support of the Institute's missions. OSPFM serves as liaison for all trans-NIAID planning and financial management activities and works with the NIH Office of the Director to ensure that the Institute has a long-range, sustainable vision and program plan for carrying out its mandate.

OSPFM directs and coordinates the activities of the following offices, branches, and operations.

- The **Knowledge Management Office (KMO)** serves the executive officers of OMO and their staffs by arranging access and delivery of information critical to the daily operations of NIAID. Together with other OMO offices, the KMO manages access, planning, and infrastructure for knowledge repositories and assets. The KMO also arranges for the ongoing management and oversight of the Institute's knowledge assets as they apply to OSPFM functions.
- The **Budget and Financial Management Branch (BFMB)** formulates, presents, and executes budgets for the \$1.5 billion AIDS program, the \$1.6 billion biodefense program, and the \$1.3 billion immunologic and infectious diseases program. BFMB analyzes, reviews, and approves grant financial plans, and develops financial content and data management tools.
- The **Mission Planning and Integration Branch (MPIB)** translates research actions and agendas to project long-term financial and capital asset needs, including human capital, and to develop integrated long-range mission plans. MPIB also conducts long-range statistical analyses and modeling to support scientific program operations and initiatives and to inform decision making.
- The **Strategic Planning and Evaluation Branch (SPEB)** provides institutional leadership for trans-NIAID strategic planning, and conducts assessments of research programs and recommends subsequent activities. SPEB determines and updates information about the state of science and emerging scientific opportunities and barriers.
- The **Office of Technology Development (OTD)** supports NIAID's intramural and extramural research programs by facilitating collaborations between NIAID researchers and external research and development organizations. OTD's staff utilizes scientific, legal, and business expertise to negotiate agreements with universities, small biotechnology companies, large national and multinational pharmaceutical companies, and other government agencies. OTD manages NIAID's portfolio of patents and inventions and serves as NIAID's resource for all issues concerning intellectual property. OTD facilitates receipt of Cooperative Research and Development Agreement funds, supports NIH's licensing program, tracks license royalty receipts, and provides NIAID investigators with training on NIH technology transfer policies and regulations. OTD coordinates NIAID's interactions with NIH's other Institutes and Centers on technology transfer issues, and is an active participant in many committees that develop and implement NIH technology transfer policy.
- The **Offices of Chief Information Officer and Technology Information Systems** include the Office of the NIAID Chief

Information Officer (OCIO) and the Office of Technology Information Systems (OTIS). OCIO provides leadership and direction of effective strategies, policies, executive responsibilities, and standards for technology services; support for biomedical research programs; and administration of information technology resources. These activities are crucial to the broadened, expanded, and intensified role of technology in support of NIAID's mission. The CIO is also the Director of the Office of Technology Information Systems.

OTIS manages and administers technologies that support NIAID biomedical research programs. The Office provides a spectrum of management, technologies development, applications/software engineering, bioinformatics support, and professional development. OTIS works closely with NIAID intramural, extramural, and administrative staff to provide technical support, liaison, coordination, and consultation on a wide variety of ventures. These projects and initiatives are aimed at ensuring ever-increasing interchange and dissemination of scientific information within the Federal government and among NIAID-supported biomedical researchers worldwide.

OTIS directs and coordinates the activities of the following branches and programs:

- The **Bioinformatics and Scientific IT Program (BSIP)** provides leadership in fields related to bioinformatics, with special emphasis on NIAID needs and requirements. This program helps coordinate scientific and technological expertise for planning, forming partnerships with researchers, and assisting with lab projects. Specific emphasis areas include high-performance super-computer cluster resources and biocomputing consulting involving structural biology, phylogenetics, and biostatistics.
- The **Scientific Applications and Information Systems Branch (SAISB)** provides core cyber technologies research, development, and engineering of applications in support of NIAID biomedical research. SAISB services include formulating, designing, developing, implementing, executing, maintaining, and evaluating technology including applications, services, and systems. Using contemporary management standards and best practices, analysts and information technology developers respond to researcher and administrator requests. These activities involve the management of software, systems, and applications.
- The **Extramural Services Branch (ESB)** provides cyber technologies technical management and support for the Institute's extramural biomedical research program administration, including support to off-campus administrative offices, extramural biodefense research, and allied programs. ESB manages operational testing, implementation, technical maintenance, security, and user support for applications and systems employed in research program administration. ESB provides essential services to facilitate local area network/wide area network (LAN/WAN) connectivity, NIAID telework, and a collegial, authorized, and accessible framework for automated information sharing and collaboration.
- The **Intramural Services Branch (ISB)** provides technical management and support for the cyber technologies used in NIAID intramural biomedical research programs, including technology support

to intramural biodefense research. ISB's activities on behalf of the intramural research community parallel those of ESB for the extramural research community. In addition, ISB supports the Rocky Mountain Laboratories and NIAID programs at Fort Detrick, Maryland, and other continental U.S. operations.

- The **Policy and Resources Management Branch (PRMB)** is responsible for oversight, policy, and guidance of cyber technology programs throughout NIAID. PRMB provides coordination for technology-related policy, strategic planning, capital planning and investment control, governance, technology acquisitions, administration, and alignment of resource administration with NIAID biomedical technologies programs. PRMB enhances human resources professional development through inservice training, professional development activity in the laboratories, and collaboration with interdisciplinary professionals.
  - The **Office of Workforce Effectiveness and Resources (OWER)** advises the leadership of NIAID on organizational performance, effectiveness, and efficiency. OWER conducts human capital oversight, including Title 42, Title 5, and performance management; workforce planning; recruitment; and paid advertising. OWER also oversees learning and development programs for the Institute and facilitates internal communications, including OD/DIR Intranet development and newsletters.
- OWER directs and coordinates the activities of the following branches:
- The **Workforce Management Resources Branch (WMRB)** assists NIAID senior managers in assessing organizational and programmatic human capital requirements. WMRB helps broker and implement human capital solutions for the NIH Office of Human Resources and other appropriate offices and staff.
  - The **Workforce Retention and Development Branch (WRDB)** advises NIAID senior leadership on ways to measure the success of the organizational structure and assists senior managers in the areas of learning, development, and change management to enhance overall organizational capability and talent development. WRDB provides leadership, oversight, and guidance for learning and development initiatives, including business process improvement and internal Institute communications.
  - The **Division of Clinical Research** replaces the Office of Clinical Research, formerly a component of the OD. A description of the newly established Division will appear in the FY 2006 Profile.

## OUTREACH ACTIVITIES

An important part of NIAID's mission is to disseminate research results to the media, health professionals, and the general public and to recruit volunteers into clinical trials of potential disease treatment and prevention methods. Several NIAID divisions and offices initiate and participate in targeted outreach activities. These activities include producing and disseminating print, audiovisual, and Web-based materials; distributing materials at professional and community meetings; and sponsoring workshops, seminars, and conferences for the media, health professionals, researchers, and the general public.

In FY 2005, the NIAID Office of Communications and Public Liaison (OCPL), renamed the News and Public Information Branch, produced materials on allergic, immunologic, and infectious diseases as well as potential illnesses caused by agents of bioterrorism. The NIAID Web site, which is visited approximately 800,000 times each month, contains a wealth of information about NIAID's organization, laboratories, and research programs. It also contains health information on many NIAID research topics. Web users looking for health information can download and/or request NIAID printed materials. ([www.niaid.nih.gov](http://www.niaid.nih.gov))

In FY 2005, OCPL published two new health information products, available in print and online: Tuberculosis: Getting Healthy and Staying Healthy (<http://www.niaid.nih.gov/publications/tb.htm>) and Is It a Cold or an Allergy? (<http://www.niaid.nih.gov/publications/flu.htm>). Both are also available in Spanish.

Scientific and health-related meetings are important vehicles for OCPL's outreach efforts. Institute staff members distribute materials and answer questions about NIAID research, training, and job opportunities at conferences, including those sponsored by the American Academy of Allergy, Asthma and Immunology; American

Society for Microbiology; Infectious Diseases Society of America; and Annual Biomedical Research Conference for Minority Students.

An OCPL communications initiative continues to expand Institute efforts to keep hundreds of voluntary and scientific organizations updated about Institute activities. Periodic e-mails provide timely news on NIAID research advances that relate to the specific research interests of each organization. In addition, OCPL disseminates NIAID news through the *NIH Public Bulletin* (<http://getinvolved.nih.gov/newsbulletins.asp>).

OCPL is involved in outreach activities related to the construction of several NIAID-funded biosafety laboratories. Most prominent among these activities is the neighbor outreach program in Hamilton, Montana, where construction of a new Integrated Research Facility is under way at NIAID's Rocky Mountain Laboratories (RML). RML has established a database of about 200 RML neighbors it can contact rapidly about ongoing RML activities, including new construction.

In October 2004, RML began distributing a monthly laboratory construction bulletin. In addition, RML staff participate in monthly construction meetings with neighbors and interested parties, and the RML Community Liaison Group meets quarterly and receives both scientific and RML development planning updates.

In FY 2005, RML coordinated two informational symposia for the community—one on pandemic influenza and the other on chronic wasting disease in elk and deer. The symposia combined the talents of State and local health experts and NIAID researchers from RML and Bethesda, Maryland, who presented information to the community and answered questions. RML also collaborated with the State public health agency to share a video of the pandemic influenza symposium with more than 50 county and

tribal health offices. A DVD of the influenza symposium was sent to the Montana Department of Public Health and Human Services to circulate to about 50 of its health jurisdictions.

In four local middle schools, RML sponsors a scientific educational program for children called “Biomedical Research After School Scholars,” or BRASS. RML displays information about its scientific mission and research in staffed booths during the Ravalli County Fair and the Bitterroot Spring Fair. Laboratory staff members give facility tours to numerous local, State, and international groups.

Through its Division of AIDS, NIAID is actively involved in educating the public about HIV vaccine research. Targeting at-risk populations, particularly African-Americans, Hispanics/Latinos, and men who have sex with men (MSM), NIAID is implementing a national education campaign to increase awareness of and support for HIV vaccine research. Specifically, the campaign is designed to

- increase awareness about the urgent need for an HIV vaccine;
- create a supportive climate for current and future HIV vaccine trial volunteers; and
- improve public perceptions and attitudes toward HIV vaccine research.

NIAID also sponsors the Community Education and Outreach Partnership Program (CEOPP). This program is designed to increase the capacity of organizations to conduct awareness and educational activities that will increase knowledge and awareness about HIV vaccine research in their targeted at-risk communities, and to foster more positive attitudes about HIV vaccine research so that communities are more supportive of and receptive to volunteering for HIV vaccine trials. In 2004, eight awards were made to national organizations and 20 were made to local community-based organizations (CBOs).

In 2005, 14 additional awards were made to CBOs located in areas where NIAID conducts HIV vaccine research. These CEOPP awardees partnered with local NIAID-sponsored HIV Vaccine Trial Units and NIAID’s Dale and Betty Bumpers Vaccine Research Center (VRC) to strengthen collaborative efforts and build capacity of CBOs to conduct HIV vaccine awareness and education activities.

Through its HIV vaccine education campaign, NIAID conducted a national survey in which attitudes and knowledge about HIV vaccine research were evaluated in the general population as well as in segmented groups of African-Americans, Hispanics/Latinos, and MSM. Results of the survey show that misinformation and distrust continue to present formidable barriers to supporting HIV vaccine research, and that low public awareness and knowledge of HIV vaccine research must be addressed to develop and sustain HIV vaccine clinical research efforts. NIAID staff used the research findings to identify key messages and formulate a campaign strategy that would be both effective and powerful. Key messages include:

- No HIV preventive vaccine is available currently;
- Only HIV-negative individuals may participate in HIV preventive vaccine trials;
- No one can get HIV from the vaccines being tested;
- Volunteers from all populations must participate in clinical trials to develop an HIV vaccine that works in each population; and
- HIV vaccines are our best hope to end the HIV pandemic.

Another major HVCC activity is coordinating activities for the annual HIV Vaccine Awareness Day (HVAD) on May 18<sup>th</sup>. HVAD was

established as a day to acknowledge and thank volunteers and researchers involved in HIV vaccine research. Community activities and media events around the country highlight research advances, address challenges associated with HIV/AIDS, and recognize volunteers who have participated in HIV vaccine clinical trials. (See page 21 for more information.)

The VRC is dedicated to basic and clinical research on the development of vaccines against HIV/AIDS and other human diseases. The VRC recruitment and outreach team is charged with the recruitment and retention of prospective volunteers into vaccine trials, production and dissemination of educational materials, and outreach to all communities, with special attention to those communities most affected by the HIV pandemic and other emerging and re-emerging infectious diseases (e.g., Ebola, West Nile virus, severe acute respiratory syndrome or SARS, etc.).

The team, which consists of two outreach coordinators and a molecular biologist, works closely with CBOs, AIDS service organizations, high schools, universities, churches, and medical establishments to increase awareness and educate the public about HIV vaccine research. The team participates in various community events, visits local and national organizations, gives presentations, and invites groups and individuals to the Center for a first-hand look. The VRC is currently supporting the Capital Area Vaccine Effort (CAVE) and the Community Education

Group (CEG). CAVE/CAB, a community advisory board, devises strategies to harness the power of people as educators, watchdogs, and advocates for volunteerism, activism, testing, and research for HIV vaccines. CEG provides information about clinical trials to minority communities, using small groups to explain how clinical trials work and why it is important for minority communities to get involved. CEG is a 2005 CEOPP awardee and has diligently integrated preventive HIV vaccine research into its program. Both organizations work closely with the VRC's recruitment and outreach team and have been instrumental in providing advocacy and disseminating information about HIV vaccines.

The recruitment team along with the clinical team strives to foster positive relationships in order to build trusted and productive community partnerships. OCPL has collaborated with the team in outreach efforts by proposing volunteer stories to local news media, helping develop marketing campaigns, and coordinating the development of informational materials for use by the VRC and the NIAID-supported HIV Vaccine Trials Network. Increasing public awareness and education are essential to sustaining clinical trial enrollment and cohort diversity. They are important factors in increasing public involvement with all aspects of HIV vaccine development and approval. Additionally, enhanced public awareness and education are of paramount importance in communities most affected by HIV.

## RESEARCH PLANNING

NIAID's long-standing tradition of rigorous research planning depends on the development and prioritization of specific research initiatives on an annual basis and on long-range strategic planning. NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report, *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health*. The research planning process derives much of its strength from two planning events, the annual Winter Program Review and the Summer Policy Retreat.

### Winter Program Reviews

NIAID's annual program reviews bring Institute scientists and senior staff together to focus on future research opportunities and to review proposed research initiatives for new and ongoing research programs.

The specific objectives of the annual program reviews are to

- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;
- Enable NIAID leaders to discuss the scientific framework for and priority of new and ongoing research programs in the context of the above factors; and
- Provide information useful in making decisions about research activities and initiatives to be implemented in the future budget year.

### Summer Policy Retreats

Annual policy retreats further enrich the planning process by providing decisionmakers with opportunities to

- Focus on broad scientific issues, opportunities, gaps, and directions;

- Identify scientific opportunities and gaps;
- Ensure that scientific planning addresses the interests and priorities of the Congress, the Administration, the Department of Health and Human Services (DHHS), and the NIH Director;
- Propose ways to respond to newly identified opportunities and needs;
- Explore the implications of changes in scientific or programmatic direction; and
- Set priorities for newly identified opportunities and needs within future budget years.

Each year, NIAID convenes scientific workshops, program reviews, and blue ribbon panels to evaluate progress and to determine future needs and opportunities for the many diseases and areas of research within the Institute's purview. The NIAID Director and each research division consult extensively with NIAID stakeholders, a diverse group that includes scientific experts, professional societies, and patient advocacy groups, and work with them to develop long-range strategic plans as well as specific research initiatives. Areas of emphasis articulated in strategic plans, as well as those identified by DHHS, NIH, Congress, the White House, and others, also help shape the Institute's decision-making and priority-setting process for new and continuing research programs.

Planning for future research initiatives is a multistep process that begins 2 years in advance of the projected implementation date. Throughout the process, the concepts for research initiatives are reviewed and refined. Concepts are first discussed internally during the annual program review, and undergo a second level of review and clearance by the National Advisory Allergy and Infectious Diseases Council. NIAID staff members then develop approved concepts into various forms of grant and contract solicitations,

which are announced to the scientific community. Proposed research projects are peer-reviewed and awarded on the basis of scientific merit, program relevance, and need.

## Strategic Planning

In 2000, NIAID developed a comprehensive strategic plan, *NIAID: Planning for the 21st Century*, which grew out of an intensive effort that included a task force of national experts. The plan described broad-based priorities to guide NIAID programs, policies, and initiatives through the next 3 to 5 years. The full text of the plan can be accessed at [www.niaid.nih.gov/strategicplan](http://www.niaid.nih.gov/strategicplan).

Since completing the strategic plan, NIAID has extended its reach through specific planning documents. The NIAID guiding principles for global health research are articulated in the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. This plan identifies short-term, intermediate, and long-term research goals to address these devastating international killers. The plan can be accessed at [www.niaid.nih.gov/publications/globalplan.htm](http://www.niaid.nih.gov/publications/globalplan.htm).

NIAID has also defined its major and growing program for biodefense research through a series of plans and agendas based on expert recommendations and an intricate strategic planning process. The biodefense program was spurred by the anthrax mail attacks of 2001. In 2002, NIAID convened the first Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research to assist in developing the *NIAID Strategic Plan for Biodefense Research*, the *NIAID Biodefense Research Agenda for CDC Category A Agents*, and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens*. In 2005, NIH issued the *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats*. This plan builds upon and extends NIAID's activities in the biodefense arena and can be accessed at [http://www3.niaid.nih.gov/about/overview/planningpriorities/RadNuc\\_StrategicPlan.pdf](http://www3.niaid.nih.gov/about/overview/planningpriorities/RadNuc_StrategicPlan.pdf).

[www3.niaid.nih.gov/about/overview/planningpriorities/RadNuc\\_StrategicPlan.pdf](http://www3.niaid.nih.gov/about/overview/planningpriorities/RadNuc_StrategicPlan.pdf).

The strategic plans emphasize basic research on microbes; host defense mechanisms; and the development of drugs, diagnostics, and vaccines. The biodefense research agendas articulate immediate and longer term goals for research on Category A pathogens, which include smallpox, anthrax, Ebola virus, plague, botulinum toxin, tularemia, Marburg virus, Rift Valley fever, and Lassa virus; and goals for research on Category B and C priority pathogens. The research agendas also address the research resources, facilities, and scientific manpower needed to conduct basic and applied research in these areas. The strategic plan and research agenda for radiological and nuclear threats focuses on medical countermeasures to assess, diagnose, and treat civilians exposed to radiation, and mitigate the harmful effects of such exposure to the greatest extent possible. The strategic plans, research agendas, and progress reports can be accessed at [www.niaid.nih.gov/publications/bioterrorism.htm](http://www.niaid.nih.gov/publications/bioterrorism.htm).

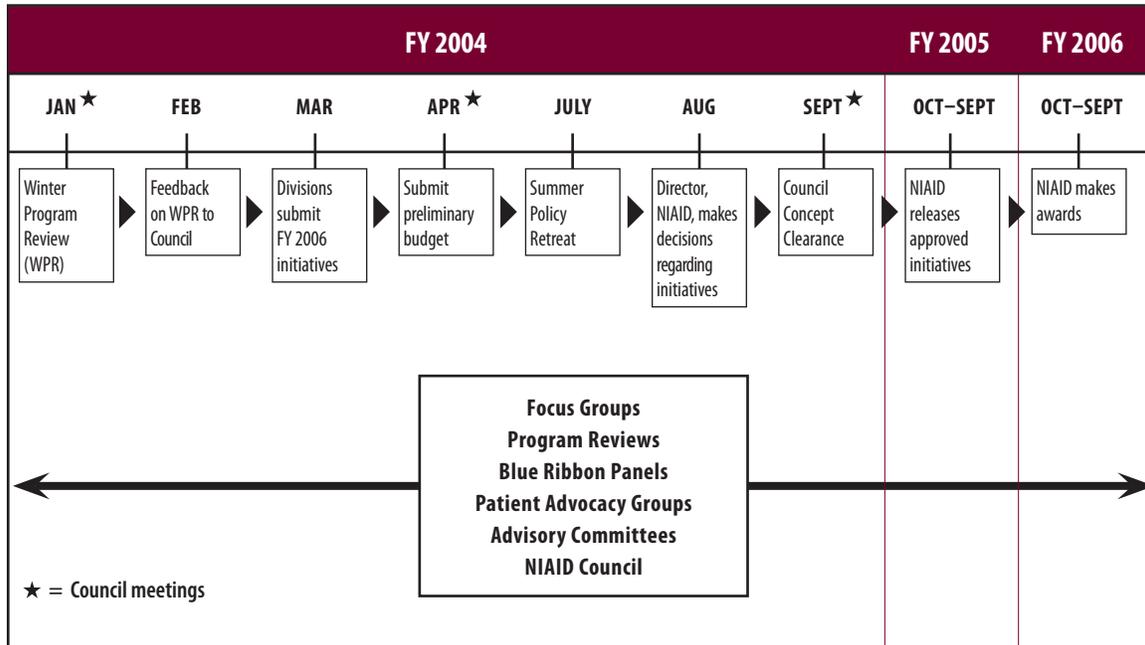
Tremendous progress has been made since these reports were first released. NIAID has increased the breadth and depth of biodefense research and has made progress in meeting the specific goals of the Blue Ribbon Panel. The *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report* describes the progress made toward addressing the immediate goals outlined in the research agenda and can be accessed at [www2.niaid.nih.gov/biodefense/research/category\\_a\\_Progress\\_Report.pdf](http://www2.niaid.nih.gov/biodefense/research/category_a_Progress_Report.pdf). The *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens Progress Report* describes the progress made toward goals outlined in its corresponding strategic plan, and can be accessed at [www3.niaid.nih.gov/Biodefense/Research/strat\\_plan.htm](http://www3.niaid.nih.gov/Biodefense/Research/strat_plan.htm).

Another important strategic planning effort focuses on how to further stimulate research activities to address health disparities. The *NIAID Strategic Plan for Addressing Health Disparities*

articulates specific action plans for reducing disparities through (1) research on HIV/AIDS, transplantation, autoimmune diseases, tuberculosis, hepatitis C virus, and sexually transmitted diseases; (2) support for research

infrastructure and research training; and (3) support for community outreach projects. The full text of the health disparities strategic plan can be accessed at [http://www.niaid.nih.gov/healthdisparities/NIAID\\_HD\\_PLAN\\_Final.pdf](http://www.niaid.nih.gov/healthdisparities/NIAID_HD_PLAN_Final.pdf).

### NIAID PRIORITY-SETTING PROCESS



## DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

### Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) was established in 1986 to help end the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of the human immunodeficiency virus (HIV), supporting the development of therapies for HIV infection and its complications and co-infections, and supporting the development of vaccines and other prevention strategies. To accomplish this, DAIDS plans, implements, manages, and evaluates programs in fundamental basic research; discovery and development of therapies and treatment strategies for HIV infection and its complications and co-infections; and discovery and development of vaccines, topical microbicides, and other prevention strategies. Staffed by over 130 employees, DAIDS comprises three main scientific programs—the Basic Sciences Program, the Vaccine and Prevention Research Program, and the Therapeutics Research Program.

### Scientific Areas of Focus

#### Basic Research

HIV pathogenesis research increases understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission. HIV pathogenesis research also supports studies of how the immune system responds to the virus. Epidemiologic and natural history research provide information about the biology and clinical course of HIV in human populations, which enhances understanding of risk factors associated with HIV transmission and progression to AIDS. Knowledge gained from these studies helps researchers develop new agents and vaccines to combat HIV infection.

Currently, DAIDS is studying the natural history of HIV progression in men and women through several cohort studies. The Women's Interagency HIV Study is a collaborative, multisite, longitudinal study designed to investigate the impact of HIV infection on women in the United States (<http://statepiaps.jhsph.edu/wihs>). The Multicenter AIDS Cohort Study (MACS) is an ongoing study of the natural history of HIV infection in homosexual men (<http://statepi.jhsph.edu/mac.html>). The MACS began in 1983 and was able to capture information about a large number of men who seroconverted while enrolled in the study. DAIDS awarded the "Tri-Service AIDS Clinical Consortium Data Analysis and Coordinating Center (TACC/DACC)" contract in late 2005. The contractor will support the TACC, a multisite natural history study of HIV infection in active duty U.S. military personnel, by providing expertise that optimizes analyses of the cohort data and fully utilizes the network of TACC clinical sites, laboratories, and specimen repositories. NIAID is also cosponsoring a new program, the Pediatric HIV/AIDS Cohort Study (PHACS), in partnership with the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, and the National Institute of Mental Health. The objective of PHACS is to address continuing critical research questions on the clinical course of perinatally acquired HIV infection in adolescents and the consequences of fetal and neonatal exposure to antiretroviral chemotherapy in a representative cohort of children from the United States. The PHACS Leadership Group was awarded this year with funding for specific protocols slated for FY 2006.

DAIDS also supports a large portfolio of investigator-initiated grants in HIV pathogenesis for a variety of areas, including mechanisms of viral entry, evasion, and replication; structure, function, and mechanism of action of viral genes and proteins; roles of cellular accessory molecules in replication; immunologic and virologic events controlling primary infection and formation of

latent reservoirs; development of *in vitro* and *ex vivo* assays to monitor virus growth, immune responses, and reservoir status during HIV disease; animal models; and genetic analysis of host factors that modulate viral infection or disease progression. These grants serve as a source of new knowledge that fuels the discovery of new drugs and vaccine concepts.

To further stimulate the pursuit of new ideas, DAIDS funds a number of targeted programs. The Novel HIV Therapeutics: Integrated Preclinical/Clinical Program is an example of how DAIDS supports the discovery, development, and evaluation of innovative HIV treatment concepts through multidisciplinary research and formal corporate partnering. The Centers for AIDS Research program, also supported by DAIDS, provides administrative and resource support and emphasizes the importance of translational research and collaborations between basic and clinical investigators.

To assist the research community and promote collaborative studies, NIAID supports the NIH AIDS Research and Reference Reagent Program, which is now in its 18<sup>th</sup> year of operation. The Reagent Program continues to provide the scientific community worldwide with a critical and unique resource of state-of-the-art biologics and chemicals useful for HIV research.

The Division's basic research efforts have yielded significant scientific information about the basic biology of HIV and the immune response to HIV infection. For example, DAIDS-funded investigators have identified the critical steps of how HIV uses the host cell machinery to enter and exit the cell, as well as the existence of multiple, persistent HIV reservoirs despite treatment with highly active antiretroviral therapy (HAART). In response, researchers are focusing their efforts on identifying new strategies to understand and eliminate these reservoirs of latent HIV. Research has also identified genetic markers that influence progression to

AIDS. Although much has been learned in recent years, questions still remain about the molecular interactions involved in the regulation of HIV expression and replication and why the host immune response is not fully effective in controlling the infection. Information about how the virus attacks the body and how the body defends itself is critical to providing additional targets against which therapeutic interventions and vaccines can be directed.

### **Therapeutics**

In order to foster the development of new HIV therapies, DAIDS supports research on potential new cellular and viral therapeutic targets, as well as new approaches to validate existing targets. The areas of research include identifying molecules that could effectively block HIV replication and control infection, improved formulations of existing agents, approaches to enhance or restore the immune system of HIV-infected individuals, molecular and genetic approaches to protect susceptible uninfected cells, combination regimens that impede the emergence of viral resistance, and assays to measure restored immunity of HIV-infected individuals. Clinical studies help determine which new agents are effective against HIV and its associated complications and co-infections, and also clarify how best to use these drugs. Investigations include basic research and drug discovery, preclinical development of candidate therapeutics, and advanced clinical testing in humans.

The evaluation of new drugs and therapeutic agents in people is a critical aspect of therapeutic research. Clinical studies define new agents that are effective against HIV and its associated opportunistic infections and co-infections and clarify how best to use these drugs. As such, DAIDS supports clinical therapeutic research in adults and children through several large clinical trials networks, including the Adult AIDS Clinical Trials Group ([www.aactg.org](http://www.aactg.org)), the Pediatric AIDS Clinical Trials Group (<http://pactg.s-3.com>), the Terry Bein Community Programs for

Clinical Research on AIDS ([www.cpcra.org](http://www.cpcra.org)), and the Acute Infection and Early Disease Research Program (<http://www.aiedrp.org>).

DAIDS-sponsored therapeutics research already has had a dramatic impact on understanding the pathogenesis and clinical management of HIV infection over the past decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped define national and international guidelines for the treatment of primary HIV infection and associated opportunistic infections and co-infections, as well as prophylactic regimens for these secondary infections; (2) identified biological and genetic markers such as CD4+ counts and viral load for predicting a drug's effectiveness and disease progression; and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-child transmission (MTCT) of HIV.

More recent studies have shown that HAART regimens, including reverse transcriptase and potent protease inhibitors, are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance or noncompliance with complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. Thus, there is an ongoing, urgent need for new therapeutic agents and regimens, new ways to boost immunity, and methods to rebuild and replace immunity lost to HIV infection. In addition, DAIDS is developing strategies to address critical questions regarding the long-term effects of antiretroviral therapy, development of drug resistance, and the most optimal approaches to medical management, especially to prevent MTCT.

### **Vaccine and Prevention Research**

The discovery and development of an HIV/AIDS vaccine to prevent HIV infection is a high

priority at NIAID. Through a balanced HIV program that integrates both basic research and empiric testing of candidate vaccines, NIAID supports a broad spectrum of research and development on HIV/AIDS vaccines. Preclinical vaccine research and development examines new vaccine concepts and approaches, as well as new ways to deliver HIV antigens in order to safely induce a potent anti-HIV immune response. Studies using animal models are aimed at defining the safety, immunogenicity, and efficacy with which the vaccine protects the host.

Clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-HIV response in people. NIAID-supported clinical trials of preventive HIV vaccines are carried out in the HIV Vaccine Trials Network (HVTN) ([www.hvtn.org](http://www.hvtn.org)). HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. Started in 2000, it has made progress towards its goal of developing and conducting a comprehensive HIV vaccine clinical research agenda that addresses scientific and public health needs and builds on scientific opportunities in the field of HIV vaccine research. HVTN has undergone significant expansion to support international trials, instituted highly functioning protocol development teams, developed new vaccine concepts and advanced new protocols, reorganized laboratory programs, and developed an extensive training program. (Additional HVTN information is located in the "Vaccine Research and Development" section on page 138.)

Vaccine research and development are supported through an extensive portfolio of investigator-initiated research in basic virology, immunology, and microbiology. Several DAIDS programs also support the interface of preclinical and clinical research. These resources stimulate the development of new vaccine concepts and ensure a rational, deliberate process for moving concepts

into and through clinical trials. Among the vaccine research programs supported by DAIDS that encourage development along various stages of the vaccine pipeline are the Innovation Grant Program for Approaches in HIV Vaccine Research Program, which encourages novel and innovative concepts in vaccine discovery and development; the HIV Vaccine Research and Design Program, which supports concepts that have evolved beyond early testing and “matured” innovation grants; and the Integrated Preclinical/Clinical AIDS Vaccine Development Program, which supports the iterative processes of vaccine concept refinement and testing. Through this program, researchers investigate promising vaccine concepts that are amenable to product development and are likely to lead to preliminary studies in humans.

In addition, HIV Vaccine Design and Development Teams, consisting of consortia of scientists from industry and/or academia, identify specific promising vaccine concepts amenable to targeted development. In response to recommendations by the Global HIV Vaccine Enterprise, in 2005, NIAID created a Center for HIV/AIDS Vaccine Immunology (CHAVI), a virtual center that will link a large group of domestic and international scientists to elucidate the correlates of immune protection against HIV and use that knowledge to design a vaccine to elicit those specific immune responses. Funded through a U01 cooperative agreement mechanism, CHAVI will support an intensive, multi-resourced, coordinated, consortium approach to address key scientific roadblocks to HIV vaccine development and to design, develop, and test novel HIV vaccine candidates, as defined by NIH and as identified by the strategic plan of the Global HIV Vaccine Enterprise. The CHAVI team is expected to be a highly collaborative, cooperative, and interactive team of leading researchers who will devote the majority of their time to the application of state-of-the-art immunological tools.

NIAID also supports comprehensive research on other non-vaccine, biomedical/behavioral prevention approaches, including the prevention of MTCT of HIV; topical microbicides; interventions such as community education and counseling that reduce behaviors such as drug abuse and unsafe sex, which expose people to HIV; programs to reduce intravenous drug abuse; measures to control other sexually transmitted infections (STIs); and antiretroviral therapies that could reduce the spread of HIV from infected people to their partners.

Non-vaccine HIV prevention research is conducted primarily through the HIV Prevention Trials Network (HPTN) ([www.hptn.org](http://www.hptn.org)). The HPTN, formed in 2000 with additional support from the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse, is a global, multicenter network dedicated to non-vaccine prevention research. Additional HPTN information is located in the “AIDS” section on page 45.

NIAID supports several research programs to facilitate the development of microbicides, including the Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM). This program is designed to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The IPCP-HTM now supports nine multi-project microbicide development efforts for novel single and combination microbicides. These efforts include pilot phase I clinical trials that support the development and evaluation of new technologies for determining microbicide safety as well as the optimization of newly identified microbicide candidates. In addition, the Microbicide Design and Development Teams (MDDT) program is designed to engage industry in the streamlined development of microbicide candidates, emphasizing combination products with multiple active agents. One award was made in FY 2005, with additional awards expected

in FY 2006, and an expansion of the program planned for FY 2007. NIAID, in coordination with the NIH Office of AIDS Research, is also developing a new microbicide research program to foster the translation of microbicide innovations to preclinical development. This novel milestone-driven program, designated the Microbicide Innovation Program, is designed to identify innovative concepts and discoveries relevant to topical microbicides and then, through a phased program of support, provide the rationale and evidence needed to determine their merit in advancing along the development path.

The Division's comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. NIAID-supported researchers have designed new vaccine strategies, modified viral antigens and vaccine vectors to improve the elicited immune response, further explained the envelope structure of HIV, advanced understanding of the role of antibody and cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes, developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies will address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. In other prevention research, new microbicides will be evaluated for their safety, acceptability, and ability to prevent the sexual transmission of HIV. Moreover, building on past research that identified an inexpensive regimen to reduce HIV transmission at birth, NIAID will continue to evaluate other practical regimens for preventing MTCT of HIV, especially during breastfeeding.

Lastly, because the majority of new infections are occurring in the developing world, NIAID's prevention and treatment research activities are conducted on a global scale. In FY 2001, NIAID launched the Comprehensive International Program of Research on AIDS (CIPRA). CIPRA provides long-term support directly to developing countries to plan and implement a comprehensive HIV/AIDS prevention and research agenda relevant to their populations and to strengthen the infrastructure required to carry out this research. Currently, there are three R03 grants, three U01 cooperative agreements, and five U19 cooperative agreements being funded through the CIPRA program in the following countries: Cambodia, China, Haiti, Malaysia, Peru, Russia, Senegal, South Africa, Thailand, and Vietnam. For more information, visit the Web site at [www.niaid.nih.gov/daids/cipra](http://www.niaid.nih.gov/daids/cipra).

### **Expanding Global Research Activities**

With the growing global impact of HIV/AIDS, there is a critical need for cost-effective prevention and treatment strategies in limited-resource regions of the world where more than 95 percent of HIV infections occur. With the explosive growth of new infections in the developing world, most of DAIDS-funded clinical research programs now have an international component. DAIDS supports research at academic and medical research centers, and collaborates with research and development companies worldwide. Many DAIDS activities support countries listed in the President's Emergency Plan for HIV/AIDS Relief, which include Cote d'Ivoire, Botswana, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia. While domestic research continues to focus on identifying the most effective treatment and prevention options for adults, adolescents, and children, internationally focused activities are designed to define global research priorities, ensure the clinical relevance of future vaccine

and prevention strategies to human populations most in need, strengthen collaborations with local investigators worldwide, and support training and infrastructure development in developing countries.

In response to the changing HIV pandemic and to expand upon and better coordinate the global research activities, NIAID is restructuring all of its HIV clinical trials research networks. In addition to increasing collaboration, efficiency, and flexibility, the new structure is designed to encourage greater integration of vaccine, prevention, and treatment research to improve upon research efforts and to address high priority research questions, particularly in resource-limited settings, where AIDS is most devastating.

### **Advisory Groups**

DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and training scientific investigators. As part of this process, DAIDS works with a number of advisory groups and community and health professional organizations to help evaluate and redirect the Division's global research programs by identifying research needs, setting priorities, and planning future programs. These advisory bodies include the Acquired Immunodeficiency Syndrome Research Review Committee (AIDSRRCC), the AIDS Research Advisory Committee (ARAC) and the AIDS Vaccine Research Working Group (AVRWG). The AIDSRRCC advises the Directors of the NIH and NIAID with respect to programs and activities in the areas of AIDS as well as the prevention and treatment of the major opportunistic infections associated with AIDS. The ARAC advises the Directors of DAIDS and NIAID on all aspects of the research portfolio, reviews progress and productivity of ongoing efforts, provides assistance in identifying critical gaps and obstacles to progress, and approves of concepts for new initiatives. The AVRWG assists in developing a comprehensive research program for expediting the discovery and development

of an HIV vaccine. A listing of ARAC and AVRWG members is located in on pages 166 and 168, respectively.

### **Collaborations**

DAIDS actively supports and promotes public- and private-sector alliances to maximize available research opportunities and resources. Its commitment to identify effective vaccine and prevention strategies and novel treatments has led to a steady increase in international activities, particularly in the developing world, where there is critical need for cost-effective prevention, treatment, and care. These efforts, in particular, necessitate collaboration with other Federal and non-Federal agencies, given the complexity of global research efforts. As a result, NIAID has forged collaborations with the Centers for Disease Control and Prevention (CDC) and Department of Defense (DoD) to bring together the vast expertise, experience, and resources of each organization and help foster coordination and efficiency. The Partnership for AIDS Vaccine Evaluation is one example of collaboration between NIAID, CDC, and DoD that was established as a way to accelerate global HIV vaccine research efforts and increase efficiency and cost effectiveness through shared laboratory capabilities, clinical trial sites, and compatibility of protocols and data. Another example is the Global HIV Vaccine Enterprise, created to foster collaboration, cooperation, and transparency in the conduct of HIV vaccine clinical trials on a global scale. The Enterprise consists of a conglomerate of international scientists and organizations committed to accelerating the development of preventive vaccines for HIV/AIDS.

### **Role of Community**

DAIDS has long recognized the importance of sustained relationships with the community, which are necessary to help foster and maintain trust and ensure that the research is designed to meet community needs. Each of the clinical research networks supported by DAIDS has

a Community Advisory Board (CAB) that works with the leadership of the network on all aspects of the research process, and other CABs that work with each individual research site. The CABs help ensure that the researchers are working in partnership with the community and help improve communications between the community and researchers. Community outreach and education are also integral components of the Division's activities. In addition, in 2001, NIAID launched its national campaign to stimulate and enhance the national dialogue concerning HIV preventive vaccines and to create a supportive environment for future vaccine studies. A steering group represents the diversity of communities affected by the AIDS pandemic and includes nationally recognized leaders in fields such as communications, the media, social marketing, community education and organizing, health care, advocacy, public policy, and HIV prevention. The campaign's activities include partnerships with national and local community groups, the development and provision of resources and materials, and advertisement and promotion of HIV Vaccine Awareness Day on May 18th of every year.

### Major Programs Supported by DAIDS

- Acute Infection and Early Disease Research Program
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- Center for HIV/AIDS Vaccine Immunology
- HIV Prevention Trials Network
- HIV Vaccine Design and Development Teams
- HIV Vaccine Research and Design Program
- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Trials Network
- HIV Vaccine Communications Campaign
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Innovation Grants for AIDS Vaccines
- Integrated Preclinical/Clinical AIDS Vaccine Development Program
- Integrated Preclinical/Clinical Program for HIV Topical Microbicides
- Microbicide Design and Development Teams
- Microbicide Innovation Program
- Multicenter AIDS Cohort Study
- Pediatric AIDS Clinical Trials Group
- Pediatric HIV/AIDS Cohort Study
- Simian Vaccine Evaluation Units
- Terry Beirn Community Programs for Clinical Research on AIDS
- Women's Interagency HIV Study

## DIVISION OF ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION

### Mission

The human immune system is composed of intricate networks of specialized cells, molecules, and organs that act together to defend the body against foreign invaders such as viruses, bacteria, and fungi that can cause disease. However, aberrant immune responses play a critical role in the development of immune-mediated diseases, which include asthma and allergic diseases; autoimmune disorders; primary immunodeficiencies; and rejection of transplanted solid organs, tissues, and cells. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

The past two decades of focused research on the immune system have resulted in major advances in understanding the mechanisms that underlie a range of immune-mediated diseases. These advances in conceptual understanding now provide realistic opportunities for improvement in the diagnosis, treatment, and prevention of many of these diseases. The Division of Allergy, Immunology, and Transplantation (DAIT) ([www3.niaid.nih.gov/about/organization/dait/default.htm](http://www3.niaid.nih.gov/about/organization/dait/default.htm)) promotes and supports a broad range of basic, preclinical, and clinical research to enhance understandings of the causes and mechanisms that lead to the development of immunologic diseases and to generate an expanded knowledge base that can be applied to the development of improved measures of diagnosis, treatment, and prevention of immune-mediated diseases. The ultimate goal of DAIT's

research program is the development of effective approaches for the treatment and prevention of immune-mediated diseases.

The Division supports research initiated by individual investigators; multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; clinical research programs to assess the safety and efficacy of new therapeutic approaches; and interdisciplinary cooperative research centers.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the treatment and prevention of transplant rejection, asthma and allergic diseases, and autoimmune diseases. Another area of program growth involves the application of emerging technologies to further understanding of immunologic principles and to develop diagnostic and prognostic tools and biomarkers of disease activity and therapeutic effect.

### Scientific Areas of Focus

#### ***Asthma and Allergic Diseases***

Asthma and allergic diseases are among the major causes of illness and disability in the United States. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses on the underlying immune mechanisms involved in these disorders and on approaches to improve diagnosis and treatment by fostering investigator-initiated projects and supporting cooperative clinical studies. In FY 2005, NIAID established the Food Allergy Research Consortium, a collaborative research program designed to develop new approaches to treat and prevent

food allergy. The consortium will conduct basic, clinical, and epidemiological studies, and develop educational programs aimed at parents, children, and healthcare providers. The Inner-City Asthma Consortium: Immunologic Approaches to Reduce Asthma Severity, a network of basic scientists and clinical investigators, was established by DAIT in FY 2002 to evaluate the efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. Current clinical trials include an Asthma Control Evaluation, the Urban Environment and Childhood Asthma protocol, and the Inner-City Anti-IgE Therapy for Asthma.

### **Autoimmune Diseases**

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the U.S. population and disproportionately afflict women. DAIT supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease. DAIT supports the Autoimmunity Centers of Excellence, which conduct collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies and mechanism-of-action studies. DAIT also supports the Centers for Autoimmune Disease Prevention, which focus on advancing knowledge for the prevention of rheumatoid arthritis and other autoimmune diseases. The goal of the Autoimmunity Prevention Centers is to develop the knowledge base necessary to design preventive interventions that could be

administered efficiently and safely. In FY 2005, the Prevention Centers supported 22 pilot projects to test innovative approaches that might lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression.

### **Basic and Clinical Immunology**

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through this research provides the knowledge base necessary to develop treatment and prevention strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary program projects on the biology of the immune system, including the basic biology of immune responses for vaccine research, transplantation immunology and chronic rejection, and autoimmunity. Clinical immunology studies focus on immune-mediated diseases, including autoimmune diseases, asthma and allergic diseases, acute and chronic transplant rejection, and immunodeficiencies. Research in these clinical areas is supported by program projects on mucosal immunity, autoimmune diseases, and methods of immune intervention.

### **Immune Tolerance**

Immune tolerance is a high priority for NIAID and, as part of a broad-based, long-range plan to accelerate research in this important area, DAIT established the Immune Tolerance Network (ITN). The ITN is an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases; asthma and allergic diseases; and rejection of transplanted organs, tissues, and cells. The goal of these therapies is to "re-educate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity

against infectious agents. The ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The ITN has established a variety of state-of-the-art core facilities and has supported 20 approved clinical protocols and several additional studies of the immune mechanisms that lead to development, maintenance, or loss of clinical tolerance. Currently, the ITN supports seven clinical trials in solid organ and islet transplantation and two cohort studies to better understand the immune mechanisms involved in the acquisition of spontaneous tolerance to organ grafts. More information about the ITN is available on its Web site at [www.immunetolerance.org](http://www.immunetolerance.org).

### **Primary Immunodeficiency Diseases**

Primary immunodeficiency diseases are caused by intrinsic defects in the cells of the immune system and are often due to inherited genetic defects. NIAID-supported research focuses on understanding the causes and immune mechanisms leading to the development of primary immunodeficiency diseases. This includes identifying pathogenic gene mutations and other contributing etiologies; expanding the genetics knowledge base to improve diagnosis and facilitate genetic counseling and decisionmaking for affected individuals; and providing protective and curative treatments, including gene therapy. In FY 2003, NIAID, with cosponsorship from the National Institute for Child Health and Human Development, established the Primary Immunodeficiency Diseases Consortium. The consortium (1) provides leadership and mentoring; facilitates collaborations; enhances coordination of research efforts; and solicits, reviews, and makes awards for pilot or small research projects; (2) maintains a primary immunodeficiency diseases registry, which provides data to

the research community about the clinical characteristics and prevalence of these diseases; and (3) develops a repository of specimens from subjects with primary immunodeficiency diseases. The consortium has funded 16 research proposals and continues to review 4 to 8 new proposals 3 times each year. Additional information on consortium activities is available on its Web site: [www.usidnet.org](http://www.usidnet.org). NIAID also supports research in large animal models of primary immunodeficiency diseases, as well as clinical trials to determine the most efficacious bone marrow transplantation regimens in patients with these diseases.

### **Transplantation**

The Division's research in transplantation immunobiology is focused on understanding the mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells; developing preclinical models to evaluate promising therapies to prevent and treat graft rejection; conducting clinical trials of new therapeutic agents and approaches to improve graft survival and function; and understanding the pathogenesis of chronic graft failure and developing new treatments and preventive strategies. Clinical research to evaluate new therapeutic approaches to improve kidney engraftment and survival is carried out through the Cooperative Clinical Trial in Pediatric Kidney Transplantation. In FY 2005, NIAID and the National Heart, Lung and Blood Institute established Clinical Outcome of Live Organ Donors, a program of epidemiologic research focused on the medical and functional outcomes of individuals who have donated a kidney or a lobe of lung for transplantation into an individual with end-stage organ failure. This program supports a consortium consisting of multiple clinical transplant centers and a Data Coordinating Center.

## Primary Research Areas

### ***Asthma and Allergic Diseases***

- Asthma and Allergic Diseases Research Centers
- Inner-City Asthma Consortium
- Food Allergy Research Consortium
- Immune System Development and the Genesis of Asthma
- Atopic Dermatitis and Vaccinia Immunization Network

### ***Autoimmune Diseases***

- Autoimmune Diseases Prevention Centers
- Autoimmunity Centers of Excellence

### ***Basic and Clinical Immunology***

- Cooperative Centers for Translational Research on Human Immunology and Biodefense
- Hyperaccelerated Award/Mechanisms in Immunomodulation Trials
- Large Scale Antibody and T Cell Epitope Discovery Program
- Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations

- Population Genetics Analysis Program: Immunity to Vaccines/Infections
- Emerging/Re-emerging Infectious Diseases
- Immune Epitope Database and Analysis Program
- Innate Immunity Receptors and Adjuvant Discovery

### ***Immune Tolerance***

- Immune Tolerance Network
- Innovative Grants on Immune Tolerance
- Nonhuman Primate Immune Tolerance Cooperative Study Group

### ***Primary Immunodeficiency Diseases***

- Primary Immunodeficiency Diseases Consortium

### ***Transplantation***

- Cooperative Clinical Trial in Pediatric Kidney Transplantation
- Clinical Trials in Organ Transplantation
- Genomics of Transplantation Cooperative Research Program
- Clinical Outcomes of Live Organ Donors
- Clinical Islet Transplantation Consortium

## DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

### Mission

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually every human infectious agent (except HIV), including pathogens used as agents of bioterrorism. DMID supports a wide variety of projects spanning the spectrum from basic research through applied research, along with the development and clinical evaluation of new drugs, vaccines, and diagnostics. NIAID also funds projects to sequence the full genomes of medically important microbes, which can be exploited in many ways—for example, to trace microbial evolution, to locate targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

Research areas in basic bacteriology and mycology include molecular structure and function, genetics, biochemical composition, and physiologic and biochemical processes. Studies of these pathogens extend basic insights to identify vaccine candidate antigens and drug targets, and also describe mechanisms of infection, pathogenicity, and virulence. Areas of particular interest include anthrax, streptococci, pneumonia, nosocomial (hospital-acquired) infections, tularemia, fungal infections, antibiotic resistance, plague, bacterial sexually transmitted infections, botulinum toxin, and bacterial diarrheas.

Research areas in virology include molecular structure and function, genetics, synthesis, and mechanisms of viral reproduction; characterization of viral proteins and nucleic acids; mechanisms of pathogenicity, latency, persistence, and reactivation; interactions with immune systems; and vaccine development. Basic research information is being used to combat important viral diseases such as influenza, smallpox, herpes, congenital cytomegalovirus

infection, viral hemorrhagic fevers, hepatitis, and viral diarrheas.

Research on parasites involves the application of biochemical, genetic, and immunologic approaches. Studies of parasites are leading to the identification of protective and diagnostic antigens, and to the development of more effective drugs. In addition, studies of arthropod vectors are aimed at controlling the transmission of important pathogens such as the malaria parasite.

One of the primary goals of the Division is to develop new and improved vaccines and strategies for vaccine delivery for the entire spectrum of infectious agents including bacteria, viruses, fungi, and parasites. Since 1981, DMID has supported a program for the accelerated development of new vaccines to direct advances in molecular biology, immunology, genetics, and epidemiology. An integral component of these efforts is vaccine safety, which is evaluated in every vaccine clinical trial sponsored by NIAID.

DMID also supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. Examples include diagnostic tests for sexually transmitted infections (STIs) and Lyme disease and the development of antimicrobial resistance markers.

Finally, DMID maintains a drug development program that supports research at three levels: drug discovery (accomplished by screening and by targeted molecular research), preclinical evaluation (in animal models of human infections), and clinical trials (evaluation of new therapies in humans).

### Scientific Areas of Focus

#### *Biodefense*

As concern grows about the use of biological agents in acts of terrorism and war, federal agencies are evaluating and accelerating the development of countermeasures to protect the

public from the health consequences of such an attack. Our ability to detect and prevent infections that emerge as a result of bioterrorist incidents depends to a large degree on the state of biomedical science. Basic and applied research supported by the NIH complements the efforts of other federal agencies by developing the essential tools—diagnostics, therapeutics, and vaccines—that are needed by physicians, nurses, epidemiologists, and other public health workers to prevent and control outbreaks of disease. NIAID is the primary NIH Institute that supports and conducts research on the diagnosis, prevention, and treatment of infections caused by a wide variety of emerging pathogens, including those that could be intentionally introduced.

In response to the need for rapid development of resources for biodefense, NIAID continues to expand its research related to potential agents of bioterrorism as part of a broad research agenda involving other agencies within the Department of Health and Human Services and the Department of Defense. The components of the NIH's biodefense research program include the development of biodefense-relevant diagnostics, therapeutics, and vaccines, as well as genomics, basic research on potential agents of bioterrorism, and infrastructure to support advanced research. Recent NIAID programmatic accomplishments include support for bioinformatics and proteomic resource centers; expansion of the Vaccine and Treatment Evaluation Units to accommodate testing of vaccines such as those for smallpox and anthrax; development of several new animal models for diseases caused by NIAID Category A, B, and C agents; support for grants and public-private partnerships for early product development through clinical trials of biodefense vaccines and drugs; a centralized repository to acquire, authenticate, store, and distribute NIAID Category A, B, and C agents to the scientific community for use in research and product development; and the continued expansion of research capacity through the multimillion dollar Research Centers of Excellence and National and

Regional Biocontainment Laboratories across the United States, which will provide critical resources for biodefense and emerging infectious disease research.

### **Emerging and Re-emerging Infectious Diseases**

Emerging infectious diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence. Recent outbreaks of severe acute respiratory syndrome (SARS) and avian influenza in Asia and monkeypox in the United States are examples of emerging infectious diseases, whereas tuberculosis and pertussis are examples of diseases that have re-emerged after a period of decline. Factors involved in the emergence and re-emergence of infectious diseases include evolution of microbes; changes in compliance with vaccination guidelines; overuse of antimicrobials; and changes in the interactions between humans and the environment due to human population growth, density, and contact with animal vectors or animals that may serve as disease reservoirs.

Both emerging and re-emerging diseases have significant implications for domestic and global health. DMID supports a broad spectrum of basic research on infectious diseases, including studies of epidemiology; pathogenesis; transmission and microbiology of emerging infectious diseases; and applied and clinical studies to develop and test vaccines, diagnostics, and therapeutics for these diseases. Examples of DMID-supported research on emerging infectious diseases include robust research programs in influenza, SARS, West Nile virus, and Lyme disease. In 2003, DMID established multiple Research Centers of Excellence, and National and Regional Biocontainment Laboratories across the United States, where scientists will be able to safely conduct critical research on emerging infectious

diseases and NIAID Category A, B, and C priority agents.

### **Vaccine Research and Development**

DMID supports an active program of basic and applied research for the accelerated development of new vaccines, taking advantage of advances in molecular biology, immunology, genetics, and epidemiology. Research conducted under this program contributes to the development of new vaccines for a wide variety of bacterial, viral, and parasitic diseases, including SARS, malaria, influenza, West Nile virus, herpes, pneumonia, and whooping cough. DMID also supports research to develop novel vaccine delivery methods, such as transcutaneous skin patches and nasal vaccines. Additionally, DMID supports a large national and international network for clinical trials of safety and efficacy of vaccines. Recent expansions of the network will allow more trials focused on specific populations and larger clinical trials, including those for biodefense vaccines. DMID's *The Jordan Report*, now in its 20th anniversary edition, is a unique resource developed by the Division to inform the public health community and the general public of recent developments and the state of the science in vaccine research. This report can be viewed online at [www.niaid.nih.gov/dmid/vaccines/jordan20](http://www.niaid.nih.gov/dmid/vaccines/jordan20).

### **Antimicrobial Drug Resistance**

Emergence of drug-resistant infectious agents is becoming an increasingly important public health concern. Rapid evolution of microbes and misuse of antibiotics are major contributors to the rising number of resistant pathogen strains. Tuberculosis (TB), gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat because of the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired infections. More than 70 percent of the bacteria that cause hospital-acquired infections

are resistant to at least one of the drugs most commonly used to treat them (see the Centers for Disease Control and Prevention. *Campaign to Prevent Antimicrobial Resistance in Healthcare Settings* online at: [www.cdc.gov/drugresistance/healthcare/problem.htm](http://www.cdc.gov/drugresistance/healthcare/problem.htm)). Also, drug resistance that was almost exclusively hospital- or health care-associated is appearing and originating with increasing frequency in the community, such as community-acquired, methicillin-resistant *Staphylococcus aureus*. Many physicians are concerned that several bacterial infections soon might be untreatable with currently available drugs.

NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens, including antimicrobial resistance among the major health care-associated bacterial pathogens. Specifically, NIAID supports investigator-initiated research on the molecular mechanisms responsible for drug resistance, as well as research to develop and evaluate new or improved therapeutics for disease intervention and prevention. Studies on several key organisms of interest seek to define how bacterial pathogens acquire, maintain, and transfer antibiotic-resistant genes. In August 2004, NIAID held the second Summit on the State of Anti-Infective Development to address the important issue of antimicrobial availability and to help determine the best ways for NIAID to address the key needs. (See [http://www.niaid.nih.gov/dmid/meetings/anti\\_infective\\_mtg\\_2004.pdf](http://www.niaid.nih.gov/dmid/meetings/anti_infective_mtg_2004.pdf) for more information about the 2004 summit.) More recently, NIH sponsored a study by the National Academy of Sciences to generate ideas for innovative research approaches that would contribute to the development of new antimicrobial therapeutics. The report resulting from this study, *Treating Infectious Diseases in a Microbial World*, suggests several promising new avenues of research that could revolutionize the field of antimicrobial/anti-infective development.

NIAID also continues to participate in an interagency task force for the development of public health strategies to address antimicrobial resistance. *A Public Health Action Plan to Combat Antimicrobial Resistance*, developed by the task force, describes issues, goals, and action items in surveillance, prevention and control, research, and product development, as well as a plan for interagency and industry coordination in addressing this critical health issue. The action plan is available online at <http://www.cdc.gov/drugresistance/actionplan>.

### **Global Health**

Infectious diseases pose a major public health challenge not only in the United States, but worldwide. NIAID research is based on the view that we live in a global community; we cannot separate the health problems of the United States from those of the rest of the world. Thus, the Institute seeks to create more effective means to prevent, diagnose, and treat infectious diseases of international importance by improving vaccines, diagnostics, and therapeutics that can be used in the developing world. This requires addressing special scientific and logistical challenges, such as accessing endemic sites and populations.

Scientists studying genomics, microbial physiology, epidemiology, natural history, disease transmission and progression, and vector control all contribute to NIAID's efforts to tackle infectious diseases on a global scale. The Institute supports laboratory, field, and clinical research through disease-specific initiatives, investigator-initiated grants, and special programs, such as the International Collaborations in Infectious Diseases Research (ICIDR) and the Tropical Medicine Research Centers (TMRCs). Both ICIDR and TMRC programs cover a broad spectrum of infectious diseases including respiratory, enteric, viral, and parasitic, as well as emerging diseases and sexually transmitted infections. These programs establish collaborations between scientists from the United States and those in host countries to address

problems paramount to local communities, expand the expertise of U.S. and foreign scientists, and strengthen the academic base of the host institution. NIAID also offers small research grants that are specially designed to provide an entry point for investigators in developing countries to get NIH funding.

TB and malaria are two components of NIAID's extensive global health research portfolio. Together, these two diseases account for tremendous morbidity and mortality throughout the world. NIAID's TB research includes studying basic biology of drug-resistant and nonresistant strains, disease progression, diagnostics, vaccines, therapeutics, epidemiology, and genomics. The NIAID Tuberculosis Research Unit supports an international, multidisciplinary team of collaborators to translate basic research findings into the development of clinically useful products. Current research activities sponsored by NIAID for malaria include drug development, pathogenesis research, vaccine development, epidemiology, and vector control, as well as the Malaria Research and Reference Reagent Resource (MR4) Center, a repository that supports malaria research throughout the world.

### **Sexually Transmitted Infections**

Sexually transmitted infections are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with HIV/AIDS. Scientists now believe that people who have STIs are at an increased risk of contracting HIV/AIDS. DMID's STI research emphasis is on vaccine development, as well as clinical, epidemiologic, and behavioral investigations directed toward strategies for primary and secondary prevention of STIs and conditions associated with having STIs, including pelvic inflammatory disease, infertility, tubal pregnancy, cervical cancer, fetal wastage, premature birth, congenital infection, and the spread of HIV.

NIAID supports individual investigator-initiated research grants and a variety of research programs for the development of more effective prevention and treatment approaches to control STIs. Research efforts include developing and licensing vaccines, topical microbicides, and treatments for STIs; understanding the long-term health impacts of sexually transmitted pathogens in various populations; stimulating basic research on the pathogenesis, immunity, and structural biology of these pathogens; and developing better and more rapid diagnostics. Specific programs supported by NIAID include the Sexually Transmitted Disease Cooperative Research Centers, which bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. Another program, the STI Clinical Trials Unit, conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STIs. Finally, the Topical Microbicides Program supports basic research, product development, and clinical evaluation activities aimed at developing female-controlled barrier methods for the prevention of STIs and HIV/AIDS infection.

### **Pathogen Genomics**

In 1995, the first microbe-sequencing project, *Haemophilus influenzae* (a bacterium causing upper respiratory infection), was completed with a speed that stunned scientists. Encouraged by the success of this initial effort, researchers have continued to sequence an astonishing array of other medically important microbes. NIAID has made a significant investment in large-scale sequencing projects and projects to sequence the full genomes of many human pathogens, including those that cause tuberculosis, anthrax, plague, gonorrhea, chlamydia, cholera,

pneumonia, aspergillosis, malaria, and influenza. In addition, NIAID collaborated with other funding agencies to sequence larger genomes of pathogenic fungi, protozoan pathogens such as the organism causing malaria, and invertebrate vectors of infectious diseases.

The availability of microbial and human DNA sequencing in publicly accessible databases has opened up new opportunities and allowed scientists to conduct functional analyses of genes and proteins in whole genomes and cells, as well as studies of the host immune response and an individual's genetic susceptibility to pathogens. When scientists identify microbial genes that play a role in disease, it paves the way to design drugs to block the activities controlled by those genes. Because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins, or to design candidate vaccines based on the proteins. Comparative genomic analysis of microbes also can be used to study the spread of a virulent or drug-resistant form of a pathogen.

NIAID is committed to continuing its support for projects to sequence the genomes of microbes, as well as increasing its support for functional genomics and proteomics, decoding sequence information, and determining its functional sequence. Moreover, NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community and to supporting the development of bioinformatic and computational tools and databases to allow investigators to have easy access to sequence and functional data for the functional genomic analysis of microbial pathogens. In summary, DMID supports a breadth of research activities on a variety of pathogens important in basic microbiology and infectious diseases.

## DIVISION OF INTRAMURAL RESEARCH

### Mission

The Division of Intramural Research (DIR) ([www3.niaid.nih.gov/about/organization/dir/default.htm](http://www3.niaid.nih.gov/about/organization/dir/default.htm)) conducts laboratory and clinical research covering a wide range of biomedical disciplines related to infectious diseases, immunology, and allergy. DIR scientists conduct basic laboratory investigations to understand the biology and genetics of the viruses, bacteria, protozoa, and other microbes that cause infectious diseases, as well as the ticks, mosquitoes, fleas, and flies that transmit them. They also study the multitude of cells, antibodies, proteins, and chemicals that compose the immune system. A fundamental understanding of the immune system is key to the development of therapies and vaccines for infectious diseases, and to deciphering and treating immunological disorders ranging from mild allergies to life-threatening immunodeficiencies.

DIR expertise is being applied to meet the challenge of emerging infectious diseases, such as avian influenza and West Nile fever, and to develop defensive measures against bioterrorism. In FY 2005, the DIR's long-term investments in viral vaccine development and poxvirus research paid important dividends, as vaccines for pandemic influenza and West Nile fever and diagnostics and therapeutics for smallpox progressed to advanced stages of development.

In addition, the DIR has a large program focused on investigations of prion diseases, such as "mad cow" disease and chronic wasting disease of deer and elk, which are caused by a transmissible agent that has little in common with conventional infectious microbes.

The ultimate goal of the Division's research is to contribute to the development of new and improved therapies, diagnostics, and vaccines that

will improve health, save lives, and enhance the quality of life of people in the United States and throughout the world. This contribution might take the form of delineating a cell-signaling pathway, discovering the function of a tick gene, determining the three-dimensional structure of an immune cell receptor, or finding the enzyme malfunction causing a primary immunodeficiency disease.

### Beyond the Laboratory

Though investigator-initiated basic research continues to be the mainstay of the NIH intramural program, today greater emphasis is being placed on translating laboratory research findings to the clinical arena. On the NIH campus, this is accomplished through the facilities of the NIH Clinical Center, the world's largest clinical research complex. There, physician-scientists treat patients with a variety of diseases, including AIDS, host defense defects, asthma, various parasitic diseases, and disorders of inflammation. NIAID currently has more than 80 active clinical protocols, under which patients participate in studies of new and promising treatments or diagnostic procedures, often derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the stimulating scientific setting of the NIH while they participate in DIR's basic and clinical research programs.

The DIR and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

## Scientific Resources

Each of the 18 DIR laboratories ([http://www3.niaid.nih.gov/about/organization/dir/lab\\_des.htm](http://www3.niaid.nih.gov/about/organization/dir/lab_des.htm)) has project-specific resources that are augmented by the expertise and services provided to all DIR labs by supporting branches. The DIR branches offer access to state-of-the-art technologies for peptide synthesis, protein sequencing, mass spectroscopy analysis of peptides and small molecules, electron microscopy, confocal microscopy, flow cytometry and cell sorting, yeast 2-hybrid screening, and DNA microarray analysis. The branches also provide genetically modified (transgenic as well as knockout/knockin) mice, extensive inhouse animal breeding and holding facilities (including nonhuman primates), oversight of animal protocols, and support to scientists conducting animal studies. Animal care facilities, including biosafety level (BSL)-3 facilities, are maintained in Bethesda, MD, and at DIR laboratories in Hamilton, MT. New facilities featuring animal BSL-3 and maximum containment BSL-4 labs are under construction, with completion scheduled for early 2006 and 2007, respectively. In addition to the facilities directly managed by NIAID, DIR investigators have access to NIH-wide facilities such as the Mouse Imaging Facility.

A multidisciplinary initiative begun in 2005 aims to use a systems biology approach to develop new computer modeling and simulation resources for immunology research. This initiative will integrate knowledge about the individual genes, molecules, and cells of the immune system into a coherent whole to provide a more global understanding of physiologic function. Interdisciplinary teams of mathematicians, engineers, computer experts, biophysicists, biochemists, geneticists, and cell biologists will provide the tools and techniques necessary for quantitative, predictive modeling of immune function in particular and biological systems in general.

This scientific teamwork is made possible by up-to-the-minute computer systems and

communications resources. Computer linkages for DIR scientists include a local area network within NIAID and a wide area network linking DIR scientists in Bethesda, Rockville, and Frederick, MD, and the Rocky Mountain Laboratories in Hamilton, MT, to other NIH resources such as the National Library of Medicine. Teleconferencing equipment and direct satellite uplinks further enhance communications between DIR staff members and their colleagues across the campus and around the world. Investigators wishing to interact directly with other scientists in a focused setting can do so by joining one of the more than 80 NIH scientific interest groups organized around specialty areas.

## Scientific Areas of Focus

### Immunology Research

Immunology research is inextricably linked to studies of infectious diseases and allergy. In studying immunologic diseases, DIR scientists consider both the normal processes of the immune system and how these processes malfunction in the disease state. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system to recognize and destroy invading organisms. Second, the findings enhance the understanding and development of effective treatments for immunodeficiency diseases in which the immune cells are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Advances in immunology research in FY 2005 include:

- Discovery of the mechanisms by which caspase-8 deficiency causes both autoimmunity and combined immunodeficiency;
- Identification of *Toxoplasma* profilin as the first chemically defined ligand for Toll-like receptor 11;

- Association of autoantibodies to interferon-gamma with severe disseminated mycobacteria infections; and
- Precise identification of natural killer cells in nonhuman primates.

### **Allergy Research**

Researchers studying allergic diseases concentrate on asthma; allergic reactions involving the skin, nasal passages, and sinuses; and chronic food allergy. Much of this research focuses on mast cells, which play an important role in many allergic disorders and secrete chemicals such as histamine. Histamine is responsible, in part, for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. Accomplishments in FY 2005 include the following:

- Opening of a pediatric allergy clinic to provide a focal point for translational research conducted in collaboration with NIAID intramural laboratories;
- Determination that a molecule called GATA-3 is a key factor in allergic diseases and a rational target for new drugs to treat allergies and asthma; and
- Initiation of a clinical study to gather clinical and immunological data to characterize allergic disease onset, progression, and remittance.

### **Infectious Disease and Biodefense Research**

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing understandings of pathogenic organisms, host response to infection, vector biology, and chemotherapeutics. Studies of the microorganisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, West Nile fever, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the pathogen that are necessary for reproduction. Host studies can define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies can reveal new targets for public health interventions. Application of this multidisciplinary approach to investigations of new and re-emerging infectious diseases and biodefense research is a top DIR priority. DIR scientists are collaborating with colleagues from government, academia, and industry to develop vaccines, diagnostics, and therapeutics for high-priority pathogens and to conduct the basic laboratory research that provides the foundation for product development. In addition, DIR scientists are engaged in collaborative research in a number of developing countries with a high infectious disease burden. Additional information about DIR studies of biodefense research and emerging infectious diseases can be found on pages 61 and 84, respectively. Accomplishments in 2005 include the following:

- Identification of a pediatric respiratory syncytial virus vaccine candidate that is safe and stimulates a protective immune response in young infants;
- Development of the most potent anthrax neutralizing monoclonal antibodies reported to date;

- Discovery of how hemoglobin C protects against malaria; and
- Identification of a promising new target to fight certain hospital-acquired infections.

### Vaccine Research

Candidate vaccines against many infectious agents of public health importance are undergoing laboratory and clinical testing in the DIR. These include vaccines for respiratory and gastrointestinal viruses, hepatitis viruses, and infectious agents that cause common tropical diseases such as malaria and dengue. DIR scientists also are collaborating in the development of vaccines to prevent the natural or deliberate spread of infectious diseases such as smallpox, severe acute respiratory syndrome (SARS), plague,

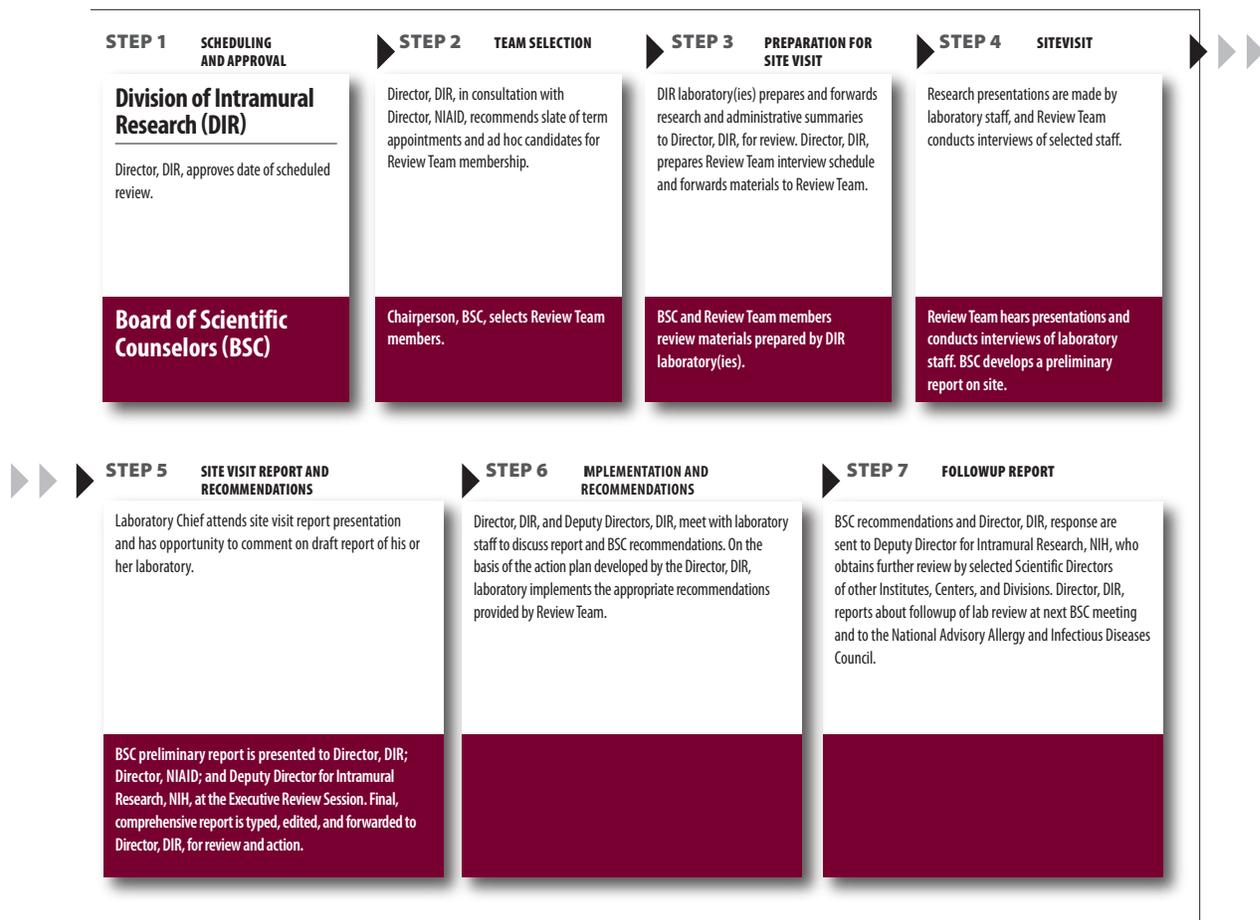
and pandemic influenza. Studies are under way to develop vaccines against pathogenic flaviviruses such as the West Nile virus, St. Louis encephalitis virus, and tick-borne encephalitis virus.

Investigations continue toward the development of a vaccine against the respiratory syncytial virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in the DIR. For accomplishments in 2005 and additional DIR information, see page 31.

### Laboratory Review Process

The following chart provides information on the DIR's laboratory review process:

## DIVISION OF INTRAMURAL RESEARCH LABORATORY REVIEW PROCESS



## DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER

### Mission

The Dale and Betty Bumpers Vaccine Research Center (VRC) (<http://www.niaid.nih.gov/vrc/default.htm>) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases. The primary focus of the VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. In 2005, 3.1 million people died from AIDS, and 4.9 million people were newly infected with HIV. Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond patients' financial reach. Therefore, effective, low-cost methods for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending the HIV epidemic.

To combat HIV, we now have at our disposal new information about the molecular and immunologic basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge may lead to new ideas and novel strategies for effective vaccines. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and

unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective HIV/AIDS vaccine. In this setting, VRC has a unique opportunity and responsibility to facilitate the translation of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

HIV strains worldwide display tremendous genetic diversity that might limit the protective immunity elicited by a single vaccine. Two types of HIV can be distinguished; these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside the region, whereas HIV-1 is the cause of the global pandemic. HIV-1 is further classified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit protective immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce effective immunity in a large percentage of those infected. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

Thus, the development of an effective vaccine against HIV is the primary mission of VRC. To this end, VRC collaborates closely with the NIAID Division of AIDS (DAIDS), particularly with regard to regulatory support and implementation of clinical trials through established trial networks. In addition to its research program for HIV/AIDS, VRC's research programs in biodefense have been expanded, intensified, and accelerated. For example, VRC, working closely with the NIAID Division of Microbiology and Infectious Diseases (DMID) and with industry partners, is positioned to make substantive contributions in the development of vaccines to protect against Category A and

B agents such as smallpox, West Nile virus, and hemorrhagic fever viruses (such as Ebola) that could pose a bioterrorist threat. VRC also is collaborating closely with DMID and the NIAID Division of Intramural Research to develop a vaccine for severe acute respiratory syndrome (SARS). In addition, VRC has recently accelerated its influenza vaccine development activities, and is developing gene-based vaccines using a prime-boost strategy against both annual and potential pandemic strains of influenza viruses.

### Scientific Areas of Focus

Historically, the process of vaccine development can be characterized as empiric, guided more by trial and error with inactivated or attenuated organisms than by rational design that builds on basic concepts in immunology and virology. Although this development process has succeeded in generating vaccines to combat numerous important infectious agents, many diseases remain for which no vaccine exists. A new science of vaccinology that takes advantage of the latest technologies and scientific knowledge to design effective vaccines is now emerging. The VRC strategic plan is predicated on the belief that development of an effective AIDS vaccine will benefit from a thorough understanding of the basis of protective immunity to the virus and the mechanisms by which HIV evades immune surveillance.

The VRC process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, has been established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis, molecular biology, and structural biology with

clinical trials methodology. Encompassing these activities at a single center possessing the capacity for vaccine production, VRC is working to advance the science of vaccine development.

The same infrastructure being employed to develop an effective HIV vaccine also is being deployed in the search for an improved smallpox vaccine, novel influenza vaccines, and for effective vaccines against Ebola, West Nile virus, and SARS.

### Basic Research

#### **Acquired Immunodeficiency Syndrome**

The VRC aims to develop vaccine candidates that will induce effective humoral responses (immune protection offered by antibodies) and cellular immune responses (immune protection offered by direct action of immune system cells). Data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the assumption that both cellular and humoral immunity are factors in preventing HIV infection or controlling HIV disease, the VRC preclinical research program explores basic science questions relevant to vaccine design.

The VRC program in virus structural biology explores the rational design of vaccines that can induce potent virus-neutralizing antibodies. Using innovative crystallographic techniques, the structure of gp120, an important viral protein on HIV's surface, has been determined at the atomic level, leading to the identification and visualization of numerous overlapping mechanisms of immune evasion. VRC is using this and other structure-based analyses and protein-based principles to assist in the rational development of novel candidate vaccines for HIV. This approach also is being applied to the development of vaccines against other pathogenic viruses of public concern.

Development of candidate vaccines focuses on using portions of engineered HIV genes to express specific HIV proteins capable of triggering a protective immune response. These genes can be delivered by immunizing with either DNA or viral vectors. In DNA immunization, the host is immunized by direct administration of viral genes. Viral vectors also can be constructed. These viral vectors transport one or more HIV genes and cause infected cells to produce HIV-specific proteins. Rodent and primate models can be used to evaluate the safety, immunogenicity (induction of immune response), and degree of protection provided by these candidate vaccines.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens (substances causing an immune response) that elicit protective immunity against HIV is guided by studies that systematically evaluate the humoral and cellular immune responses generated by vaccine candidates. The development of reproducible, validated assays to measure T cell function and virus particle reduction is key to successful evaluation of both animal studies and human clinical trials. The VRC Immunology Core Laboratory is currently designing, optimizing, and performing immunologic assays that measure cellular and humoral immune responses. Candidate vaccines are being evaluated by intracellular cytokine staining, ELISPOT assays, and measurements of neutralizing and binding antibodies. VRC also is expanding current assays to be applicable to more antigens and various clades of HIV, as well as exploring ways to optimize and automate assay performance using state-of-the-art technologies in robotics.

By using these emerging technologies, scientists can determine how effectively a candidate vaccine protects against infection or disease.

Preclinical studies in small animals and primates are used to evaluate vaccine dose,

formulation, and delivery route and to address the immunogenicity of multigene vectors and vaccine combinations. The accumulated knowledge from these preclinical studies is being used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing is integrated closely with VRC basic science and clinical programs to provide information on the advancement of promising candidate vaccines into human trials.

### **Scientists Study Previously Unobserved Characteristics of Acute HIV Infection.**

Chronic HIV infection is characterized by a steady but generally slow loss of CD4+ T cells (of both naïve and memory types). It has recently been shown that acute infection is accompanied by significant depletion of CD4+ T cells in mucosal tissues. Using a simian immunodeficiency virus (SIV) infection model, VRC scientists have shown that acute SIV infection is associated with very high rates of infection and depletion of memory CD4+ cells in multiple tissues. Extensive loss of memory CD4+ cells occurs not only from mucosal tissue but also from lymph tissue and peripheral blood. This demonstration of massive early loss of CD4+ memory T cells, an extraordinarily high loss of 24–48 percent of all memory CD4+ T cells within the first 2 weeks of infection, has critical implications for vaccine development and interventional therapies. Preventive and therapeutic strategies must be designed to prevent early and massive destruction of the memory CD4+ cell phenotype by reducing viral load during the acute phase of infection.

### **Identifying How HIV Escapes the Body's Defenses.**

One of the factors that underlies the inability to suppress HIV replication in infected individuals is that the virus mutates so rapidly that it is able to evade the T cell immune responses against it. This phenomenon, known as “immune escape,” is thought to compromise the efficacy of vaccines designed to prevent infection by priming such T cell immune responses.

VRC scientists examined the breadth of T cell repertoire, i.e., the variety of T cells that make up the cellular immune response to the AIDS virus. These researchers showed that T cell responses that are narrow in their repertoire cannot tolerate viral mutations and allow the virus to escape rapidly. Conversely, T cell responses that have a broad repertoire seem more able to tolerate mutations and thus can contain the virus more easily. These considerations are extremely important in helping to establish a framework on which to base rational design of HIV vaccines.

**New Studies Identify Mechanisms that Explain Patterns of Viral Transmission and Antibody Resistance.** Dendritic cells (DCs) normally circulate throughout tissues and lymphoid organs, where they capture antigens and process them for presentation to the immune system. DCs also capture both CCR5- and CXCR4-tropic viruses efficiently and transmit them to T cells. The envelope (Env) glycoprotein of human immunodeficiency virus type 1 (HIV-1) (gp120) is highly glycosylated, and virus attachment to DCs is mediated largely through the mannose-specific C-type lectin receptor, DC-SIGN. VRC scientists have defined a mechanism to explain preferential transmission of CCR5-tropic viruses and have shown that, although immunoglobulin G neutralizing antibodies can block CCR5-tropic HIV-1 entry into myeloid DCs, once the virus is internalized through DC-SIGN by the antigen-presenting cell, it provides a previously unrecognized mechanism of immune evasion to neutralizing antibodies that might also be integral to HIV spread and persistence. The enhancement of infection and the protection from neutralizing antibodies provided by the DCs help the virus to efficiently infect host T cells. Inactivation of HIV-1 by neutralizing antibodies at the time of initial exposure would provide a potent mechanism to inhibit HIV infection *in vivo* and would be a desirable feature of an immune response elicited by a highly effective AIDS vaccine. The enhancement of infection and the protection from neutralizing antibodies provided

by the DCs help the virus to efficiently infect host T cells. The ability of CCR5-tropic viruses to infect immature DCs allows the development of a reservoir of infected myeloid (m) DCs that infect T cells efficiently upon maturation. Preferential infection of immature mDCs by CCR5-tropic virus could serve as a cellular “Trojan horse” that initiates a persistent infection. Preferential infection of immature mDCs by CCR5-tropic virus can thus establish a pool of infected cells that can efficiently transfer virus at the same time that they protect the virus from antibody neutralization.

### **Ebola and Other Viral Hemorrhagic Fevers**

Outbreaks of Ebola in Africa kill up to 90 percent of those infected. No effective treatment exists for this highly infectious disease, which causes extensive internal bleeding and rapid death. Vaccination is regarded as the best strategy for preventing or containing this deadly infection. Investigators at VRC, with scientific collaborators at the U.S. Army Medical Research Institute of Infectious Diseases, have developed a potentially effective vaccine strategy for blocking Ebola virus infection in nonhuman primates. Previous VRC studies showed that a combination of DNA vaccination and boosting with adenoviral (ADV) vectors that encode viral proteins protected cynomolgus macaques against Ebola virus challenge and generated cellular and humoral immunity.

### **West Nile Virus**

VRC is currently developing a DNA-based vaccine against WNV in collaboration with the San Diego-based biotechnology company, Vical, Inc. The vaccine is based on an existing codon modified gene-based DNA plasmid vaccine platform designed to express WNV proteins and is being currently tested in a phase I clinical trial.

### **SARS**

In response to the recent global outbreak of SARS, VRC investigators began work immediately on

the development of a potential vaccine. The VRC contracted with Vical, Inc. to manufacture a single closed, circular DNA plasmid-based vaccine encoding the S protein of SARS-coronavirus (CoV). VRC mouse studies demonstrated that this vaccine induces T cell and neutralizing antibody responses, as well as protective immunity. A phase I open-label clinical study to evaluate safety, tolerability, and immune response was initiated in FY 2005. The study enrolled 10 healthy 18–50 years old subjects, and administered 4 mg DNA vaccinations at three 1-month intervals. Interim study results indicate that the vaccine is well tolerated and the study is expected to be complete early in FY 2006.

**Studies Shed Light on Important Genetic Differences in SARS Viruses.** Immune protection against SARS-CoV infection has been conferred by vaccination directed toward the S glycoprotein, and this effect is mediated by humoral immunity. The evolving molecular heterogeneity of SARS-CoV has raised concerns about the breadth and efficacy of protection with specific vaccine strains and the possible development of immune escape. Molecular characterization of SARS viruses has revealed significant genetic differences among isolates but the functional consequences of these differences are not well understood. VRC scientists have now demonstrated that genetic variances account for several important functional differences, such as affinity for specific viral receptors and sensitivity to antibody neutralization. These results raise concerns about the ability of SARS vaccines to contain the spectrum of SARS-CoV isolates in nature and highlight the need to develop approaches that control these genetically diverse viruses.

### **Influenza**

The VRC is exploring new approaches using novel technologies to develop a gene-based vaccine protective against influenza.

**Gene-based Vaccination Might Provide Protective Immunity Against Diverse Influenza Viruses.** Current influenza vaccines elicit antibodies effective against specific strains of the virus, but new strategies are urgently needed for protection against unexpected strains. DNA vaccines have been shown to provide protection in animals against diverse virus strains but the potency of the vaccines needs improvement. VRC scientists tested a DNA prime-recombinant adenoviral boost vaccine targeted at one of the influenza viral proteins, nucleoprotein (NP). Strong antibody and T cell responses were induced. Protection against viral challenge was substantially more potent than DNA vaccination alone. Importantly, vaccination protected against lethal challenge with highly pathogenic H5N1 virus. Thus, gene-based vaccination with NP might contribute to protective immunity against diverse influenza viruses through its ability to stimulate cellular immunity.

### **Clinical and Regulatory Infrastructure**

The VRC has assembled a full clinical research support team consisting of physicians, study coordinators, nurse practitioners, research nurses, and recruitment and outreach specialists. These staff members represent VRC at community events, screen potential volunteers, and perform vaccinations and subsequent followup and testing of enrolled volunteers. The VRC also has developed the strong regulatory infrastructure required to support the development and testing of vaccines. In collaboration with DAIDS and DMID, VRC staff members manage the submission of Investigational New Drug (IND) applications to the Food and Drug Administration (FDA), develop protocols for human clinical trials, and ensure that all studies are performed in accordance with FDA guidelines, while meeting all applicable reporting requirements.

## Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. Although animal models are invaluable for guiding the development of vaccine approaches in general, and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I and II studies in humans are required to validate safety and immunogenicity findings, and only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, VRC combines traditional empirical vaccine development with hypothesis-driven basic and preclinical research. In addition to traditional phase I studies in HIV seronegative volunteers, the VRC has been studying the ability of vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4+ and CD8+ immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will clarify mechanisms of cellular immunity and T cell memory that play a role in protection against HIV. Such data then can be applied to the development of therapeutic and preventive vaccines. To date, the VRC has conducted or collaborated with clinical networks on 19 human clinical trials.

The VRC actively collaborates with both intramural and extramural scientists and facilitates the movement of ideas from the broader community into clinical trials. Close ties are maintained with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale and international trials is already established. The VRC also maintains several strong collaborations with industry and academic partners with expertise in various areas such as DNA and viral vector production, vaccine devices and delivery, preclinical testing, and vector construction. When products emerge with promise for licensure, VRC

will continue to interact with the pharmaceutical industry, which has a large capacity for and experience in product development and distribution.

## Acquired Immunodeficiency Syndrome

The VRC's prime-boost strategy using a multigene, multiclade DNA plasmid vector prime, adenoviral vector (ADV) boost has progressed through phase I clinical trials and has entered into phase II trials. The two vaccines (six-plasmid DNA and four-vector ADV) developed by the VRC incorporate HIV genetic material from clades A, B and C, which cause about 90 percent of all HIV infections around the world. These are the first multigene, multiclade HIV vaccines to reach phase II clinical trials, marking an important milestone in the search for a single vaccine strategy that targets U.S. subtypes of HIV as well as clades causing the global epidemic. In phase I studies of the separate components, the vaccines were well tolerated and elicited cellular and humoral responses. A recently launched trio of trials (phase I/II) of this prime-boost strategy, sponsored by DAIDS, is being conducted by three international networks, the HVTN, International AIDS Vaccine Initiative, and U.S. Military HIV Research Program, to test the safety and immunogenicity of the prime-boost strategy in the Americas, Southern Africa, and Eastern Africa.

## Ebola

In November 2003, the VRC initiated the first human trial of a vaccine designed to prevent Ebola infection. All injections for the study are complete and have been well tolerated. In addition to testing preventive vaccine candidates, the VRC is currently developing a vaccine that might be useful in an acute outbreak setting. For example, a recently tested candidate (a single vector ADV-only) vaccine elicited protective immunity in monkeys after a 4-week post-vaccination challenge, in contrast to previous 10-week or 6-month vaccine regimens. A second-

generation product that would provide coverage for Marburg and possibly Lassa virus might also be evaluated.

### **MVA**

VRC is currently testing modified vaccinia Ankara (MVA) as an attenuated poxvirus with the potential to protect against vaccinia (the virus used to vaccinate against smallpox) or variola (the virus that causes smallpox). The vaccine was provided by Therion Biologics Corporation as part of a collaboration with the VRC. Two phase I clinical trials testing MVA as a component of a safer smallpox vaccine in both vaccinia-naïve and vaccinia-immune populations have recently concluded, and data will be used by NIAID to guide the design of other studies to further the development of safer smallpox vaccines.

### **New Initiatives**

NIAID has recently developed a NIAID Vaccine Immune T-cell and Antibody Laboratory (NVITAL), in Gaithersburg, MD. This new facility will perform validated immunological assays in support of phase II/III clinical studies and product licensure, and will serve as a Good Labor Practices (GLP) resource for centralized immunogenicity testing across different NIAID-sponsored vaccine projects. It is planned that this facility will support immunological analysis

activities for the VRC's recently initiated phase II international HIV vaccine studies.

The VRC has constructed a contractor-leased and contractor-operated Vaccine Pilot Plant (VPP) that will manage production of multiple vaccine candidates originating from VRC. The VPP will function in concert with the Vaccine Production Laboratory located at the Bethesda campus to transfer new vaccine technology for pilot-scale production of vaccine material for use in clinical trials. The VPP, completed in late 2005, is a self-contained facility of 126,900 square feet with the capacity to produce four to eight clinical lots of vaccine annually.

### **Human Clinical Trials and Licensure of an AIDS Vaccine**

VRC is working closely with its scientific collaborators and with FDA to discuss the potential for expedited approval of candidate AIDS vaccines. The carefully considered use of surrogate endpoints (i.e., measures of the vaccine's ability to provoke an immune response) in AIDS vaccine trials could substantially accelerate the licensure of an effective AIDS vaccine. Clinical information validating the use of surrogate endpoints can accrue from well-designed trials, and this information can be applied to the design of future trials.

## DIVISION OF EXTRAMURAL ACTIVITIES

### Organizational Overview

The Division of Extramural Activities (DEA) (<http://www3.niaid.nih.gov/about/organization/dea/default.htm>) serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts, managing NIAID's research training and international programs, and conducting initial peer review for funding mechanisms with Institute-specific needs.

In addition to providing broad policy guidance to Institute management, DEA also oversees NIAID's chartered committees, including the National Advisory Allergy and Infectious Diseases Council; disseminates information to its extramural community through its large Internet site and publications; and conducts extramural staff training and communications through the NIAID intranet.

DEA staff members interact intensively with grantees, contractors, reviewers, Council members, applicants, and staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome; the Division of Allergy, Immunology, and Transplantation; and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch (GMB) issues all NIAID grant awards after negotiating the terms of the award with grantees. GMB specialists determine award amounts, develop administrative terms and conditions, and release official award documents. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowed and how to formulate a budget for an application. GMB specialists supervise the day-to-day administration and financial management of

Institute grants and cooperative agreements, while ensuring that grants comply with existing policies.

The Contract Management Program (CMP) ([www.niaid.nih.gov/contract](http://www.niaid.nih.gov/contract)) manages the administrative aspects of NIAID's research and development contract portfolio. CMP specialists help develop requests for proposals, negotiate technical and business aspects of proposals, and select proposals for funding. Contract specialists are well versed in legal, technical, business, and cost-related topics, including Federal Acquisition Regulations. They provide investigators with guidance on changes in the scope of the research, the use of funds, and other administrative issues.

The Scientific Review Program conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications (RFAs) and requests for proposals (RFPs). Scientific review administrators assist NIAID staff members with the design, development, and review of initiatives. They also conduct initiative phasing, perform quality control of RFAs and RFPs, and formulate peer review strategies.

The Referral and Program Analysis Branch (RPAB) handles receipt and referral for grant applications that undergo initial review at NIAID. RPAB also performs scientific classification and data analysis of NIAID-funded grants, contracts, and intramural research projects for official scientific information reports.

Several offices and staff members in the DEA Office of the Director (OD) play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including innovative electronic systems. In addition, the OD is a long-time leader in

developing innovative technologies that have been adopted by the NIH, including electronic peer review and acquisition systems.

- The Office of Special Populations and Research Training (OSPRT) ([www3.niaid.nih.gov/about/organization/dea/osprtpage.htm](http://www3.niaid.nih.gov/about/organization/dea/osprtpage.htm)) manages and awards fellowships (F), institutional training (T), and research career (K) grants. OSPRT provides oversight and coordination for NIAID's minority and women's health activities and initiatives, and manages research supplements for underrepresented minorities and scientists with disabilities.
- The Office for Innovation and Special Programs ([www3.niaid.nih.gov/about/organization/dea/oisp.htm](http://www3.niaid.nih.gov/about/organization/dea/oisp.htm)) manages grants for NIAID's small business programs—Small Business Innovation Research and Small Business Technology Transfer.
- The Office of International Extramural Activities ([www3.niaid.nih.gov/about/organization/dea/oiea.htm](http://www3.niaid.nih.gov/about/organization/dea/oiea.htm)) helps develop policies for international applicants and grantees. It reviews the financial systems of non-U.S. grantees and communicates with other Federal agencies about international policies for select agents.
- The Office of Knowledge Resources (OKR) ([www3.niaid.nih.gov/about/organization/dea/okr.htm](http://www3.niaid.nih.gov/about/organization/dea/okr.htm)) informs the Institute and its extramural research community of funding opportunities, advice, policy updates, and other news. OKR provides budget and payline information as well as tutorials on NIH operations, planning and writing grant applications, and managing grant awards. The newsletter, NIAID Funding News ([www.niaid.nih.gov/ncn/newsletters/default.htm](http://www.niaid.nih.gov/ncn/newsletters/default.htm)), and the NIAID Research Funding Web site ([www3.niaid.nih.gov/researchfunding](http://www3.niaid.nih.gov/researchfunding)) are designed for the extramural research community, while the newsletters, NIAID Insider ([intra.niaid.nih.gov/organization/dea/DEA%20Express/index.html](http://intra.niaid.nih.gov/organization/dea/DEA%20Express/index.html)) and Inside Extramural ([intra.niaid.nih.gov/Organization/DEA/DEA%20Express/2006/enl021706.htm](http://intra.niaid.nih.gov/Organization/DEA/DEA%20Express/2006/enl021706.htm)), are tailored to Institute staff.
- The Committee Management Office ([www3.niaid.nih.gov/about/organization/dea/cmo.htm](http://www3.niaid.nih.gov/about/organization/dea/cmo.htm)) oversees the legal and policy requirements for NIAID's chartered committees, which include the NAAIDC, the Board of Scientific Counselors, the AIDS Research Advisory Committee, and special emphasis panels. It also administers Scientific Review and Evaluation Awards.
- The Office of Data Quality and Initiative Development ([www3.niaid.nih.gov/about/organization/dea/odqid.htm](http://www3.niaid.nih.gov/about/organization/dea/odqid.htm)) initiates, plans, designs, and oversees extramural research initiatives. It also performs review and quality control of solicited grant and contract initiatives.
- The Office of Scientific Resource Development (OSRD) ([www3.niaid.nih.gov/about/organization/dea/osrd.htm](http://www3.niaid.nih.gov/about/organization/dea/osrd.htm)) develops Web-based and classroom training for NIAID staff and expands Institute learning resources. It educates NIAID staff on key scientific, clinical, and management mechanisms to enhance job performance.
- The Office of Program Coordination and Operations ([www3.niaid.nih.gov/about/organization/dea/opco.htm](http://www3.niaid.nih.gov/about/organization/dea/opco.htm)) manages NIAID initiative phasing plans, develops NIAID Council guidance and timetables, manages the grants records center, and works with the administrative office to manage daily functional activities.



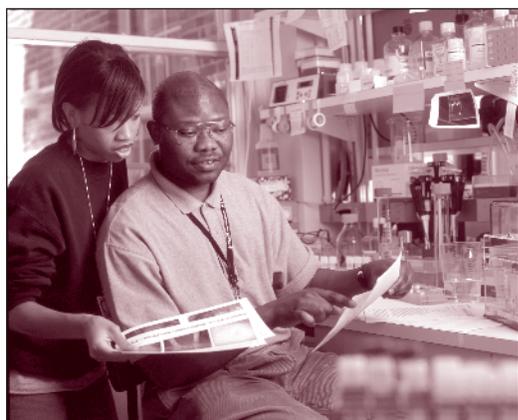
# **SELECTED AREAS OF SCIENTIFIC RESEARCH**



## ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Significant progress has been made since 1981, when mysterious cases of pneumonia led researchers to identify the disease now known as AIDS. Research has led to a better understanding of the structure of human immunodeficiency virus (HIV), which causes AIDS, how HIV attacks the immune system, the role of the immune system in controlling HIV infection, and how to intervene therapeutically. Potent therapeutic regimens, commonly referred to as highly active antiretroviral therapy, or HAART, have been successful in suppressing HIV to virtually undetectable levels in the blood and decreasing the incidence of opportunistic infections. HAART has greatly improved the quality of life of many HIV-infected people worldwide and has led to a dramatic decline in AIDS-related deaths.

Despite these scientific advances, the HIV/AIDS pandemic continues to rage around the world, with an estimated 40.3 million people living with the disease. In 2005, 3.1 million people died from AIDS, and 4.9 million people were newly infected with HIV. Of the 4.9 million new infections, 700,000 were in children. Globally, just under half of all people living with HIV are female. An estimated 40,000 people have



**NIAID research fellow** Dr. Johnan Kaleeba, of the Laboratory of Molecular Microbiology in the Division of Intramural Research, and an assistant study HIV gene regulation.

been infected with HIV each year in the United States in the past 10 years, but the epidemic is now disproportionately lodged among African Americans and is affecting much greater numbers of women.

Since the beginning of the epidemic, NIAID's comprehensive research program has been at the forefront in the fight against HIV/AIDS. NIAID supports a broad array of domestic and international HIV/AIDS research programs and collaborates with more than 40 countries through investigator-initiated research grants and multicenter prevention, vaccine, and therapeutic research networks. (See Division of AIDS Overview on page 15 for a description of programs.) With a growing number of research programs and initiatives, NIAID is poised to tackle new global research challenges as well as the changing demographics of the HIV/AIDS epidemic.

### Basic Research

Basic research in HIV pathogenesis, microbiology, immunology, virology, and animal model development lays the foundation for advancing research in HIV treatment and prevention. At NIAID, this research is conducted primarily through investigator-initiated research as well as a number of targeted programs and several large cohort studies.

This past year, as a result of advances in basic science, researchers have learned that HIV exploits a large residential population of resting memory cells in the gut-associated lymphoid tissue (GALT) to produce high amounts of virus and deplete critical memory CD4+ T cells, thereby initiating the disease process that leads ultimately to AIDS.

Several human genes have been identified as being essential for HIV infection. The most notable is the CCR5 gene, which codes for a chemokine receptor that also acts as an HIV co-receptor on the surface of susceptible

cells. Individuals with a deletion of one or both copies of the CCR5 gene are less likely to become infected with HIV. Another gene related to HIV susceptibility is CCL3L1, which encodes a protein that binds to CCR5 and blocks HIV entry into host cells. In 2005, a team of NIAID-supported scientists discovered a new twist to the story; it is not just the presence or absence of the CCL3L1 gene, but also the number of gene copies that can affect susceptibility to HIV infection and severity of HIV disease. NIAID intramural investigators added another surprise: working with a mouse model, they discovered that the CCR5 co-receptor needed for initial HIV infection and for subsequent disease progression also functions to control West Nile virus disease by helping to clear virus from the brain. This has important implications for the development of HIV inhibitors that act by blocking CCR5, because such agents, which could be helpful in treating HIV, might also render people more susceptible to the brain inflammation that can result from West Nile virus infection.<sup>1</sup>

Several investigators have recently identified a pair of gene families that encode proteins with antiviral effects. These genes are referred to as the APOBEC and tripartite motif (TRIM) families. Both gene families have multiple members. APOBEC has close to 30 and TRIM has close to 70, with the functions of all the family members not yet defined. APOBEC3G (A3G) and APOBEC3F (A3F) proteins have been shown to cause lethal mutations in HIV and other retroviruses. HIV counters the effects of these proteins through its Vif protein, which promotes degradation of A3G and A3F. Recent work by an NIAID-funded investigator has unveiled a second antiviral function of A3G that protects resting CD4+ T cells against HIV infection.

The TRIM gene family was first defined by the identification of TRIM5alpha as a factor from Rhesus macaques that had strong anti-HIV activity. Since this initial discovery, the number of

genes identified in the TRIM family has grown, and five members have been shown to have anti-HIV activity. TRIM1 and 5 work in the cytoplasm, TRIM19 and 23 appear to work in the nucleus at the time of integration, and TRIM32 works by interfering with HIV Tat. What remains to be defined is how HIV successfully mitigates the effects of these antiviral factors. Taken together, these gene products constitute a new arm of the innate immune system, the intracellular innate immune system.

NIAID scientists at the Vaccine Research Center (VRC) used a simian immunodeficiency disease (SIV) model of HIV infection to investigate the role of the virus in the depletion of memory CD4+ T cells during the acute phase of infection. Using a technique that can detect very low amounts of virus in cells, these scientists demonstrated that acute SIV infection is associated with very high rates of infection and the subsequent depletion of memory CD4+ T cells not only in mucosal tissue, but also in peripheral lymphoid tissue and blood. In fact, they found that 30 to 60 percent of CD4+ memory T cells throughout the body were infected by the virus at peak infection. In the first four days following peak infection, 80 percent of these cells were destroyed by the body, corresponding to a remarkable 24 to 48 percent elimination of *all* of the memory CD4+ T cells in this short timeframe.

The results from this study indicate that the loss of memory CD4+ T cells during acute SIV infection is considerably more marked than previously thought. The extent of the massive and rapid loss of memory CD4+ T cells throughout the body—not just in mucosal tissue where the virus typically enters the host—during acute SIV infection has critical implications for HIV vaccine development and interventional therapies. These findings indicate that preventive and therapeutic strategies must be designed to prevent early and massive destruction of the memory CD4+ T cells

by reducing viral load during the acute phase of infection.

NIAID scientists made other important basic research discoveries in FY 2005. For example, they discovered a human enzyme that is crucial to HIV replication. The process of how HIV genetic material—a long unedited strand of RNA—exits the host cell nucleus has long puzzled scientists. Human cells cut, edit, and splice RNA before it can leave the nucleus, but somehow HIV subverts that process and exports the long version of RNA that encodes instructions for making new viral particles. The researchers found that HIV uses a human enzyme known as DDX3 to straighten its RNA before threading it through small pores in the nuclear membrane. This work offers the first evidence that HIV must use this human enzyme to replicate, and suggests a potential new target for drug development.<sup>2</sup>

Intramural researchers also expanded their basic knowledge of the cytokine, interleukin-2 (IL-2), and how it functions. Intermittent administration of IL-2 to HIV-infected individuals has been found to increase the number of certain kinds of CD4+ T cells. NIAID scientists used sophisticated lab tests to track over time the fate of CD4+ T cells produced during IL-2 therapy of HIV-infected individuals. Their experiments revealed that the CD4+ T cell expansions were the result of prolonged CD4+ T cell survival, which affected both naïve and central memory CD4+ T cells without significantly affecting CD8+ T cells. These findings suggest that IL-2 can help maintain cells important for host defense against new antigens and those needed for long-term memory to opportunistic pathogens. They also demonstrate the back-and-forth nature of translational research. Years of basic lab research on IL-2 led to these patient trials, which are now increasing our basic understanding of IL-2 functioning in immune cells. This knowledge will, in turn, provide a greater foundation for understanding clinical observations in ongoing patient trials of IL-2.<sup>3</sup>

Although much has been learned, questions still remain about (1) the mechanisms of viral entry into and exit out of host cells, including the roles of cellular co-receptors and other host cell molecules; (2) the structure, function, and mechanism of action of viral genes and proteins, and how they interact with host cell genes and proteins to affect HIV replication; (3) host factors that modulate HIV transmission, replication, establishment of infection, and disease progression; and (4) the elements of the immune response to HIV during primary and chronic infection and their roles in controlling disease establishment and progression. Answering basic scientific questions about how the virus attacks the body and how the body defends itself is critical to providing additional potential targets against which therapeutic interventions and vaccines can be directed.

## Vaccine Research

An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against all HIV subtypes is critical to the effective control of the global spread of HIV. It is, therefore, one of NIAID's highest priorities, albeit one of the most difficult challenges in HIV/AIDS research. NIAID supports a spectrum of HIV vaccine research and development activities, including basic research (discovery), preclinical screening and animal model development, product development and manufacturing, and clinical research. The scope and breadth of these programs and resources continue to significantly advance global HIV vaccine development efforts.

Over the years, NIAID-supported HIV vaccine research has led to the identification of new and innovative HIV vaccine designs, improvements in vaccine delivery, development of innovative laboratory techniques and animal models for evaluating vaccines, and evaluation of over 50 vaccine candidates in clinical studies. Additional studies have already been initiated or are being planned to evaluate the safety and

immunogenicity of a range of new candidate vaccines, including lipopeptide vaccines alone and in combination with a canary pox vaccine, a Venezuelan equine encephalitis replicon vector vaccine, novel DNA vaccines, a recombinant nonreplicating adenovirus vaccine, modified vaccinia Ankara and other novel pox vector-based vaccines, a cytotoxic T lymphocytes multi-epitope peptide vaccine, and molecular adjuvants.

Notably, a NIAID-funded study provided an explanation why it is difficult to induce broadly reactive neutralizing antibodies against HIV-1. Many strains of HIV circulate worldwide, and designing HIV vaccines against the viral envelope capable of eliciting antibodies that neutralize these different strains continues to represent a major research challenge. Despite significant advances in our understanding of HIV/SIV envelope structure and function, no envelope-based vaccine has thus far succeeded in eliciting antibodies that match the breadth of the few, broadly neutralizing human monoclonal antibodies derived from long-term HIV-infected individuals. In a recent study, the authors found that not only do these human antibodies react and neutralize HIV, but they also react to cardiolipin, a lipid molecule component first isolated from heart muscle and subsequently found in the membranes of mitochondria of all cells. The implication is that these rare, broadly neutralizing antibodies might have been isolated from individuals with immune dysfunctions in whom the body makes antibodies against their own tissue molecules. This study raises many questions regarding the ontogeny of broadly neutralizing anti-HIV antibodies and the potential to elicit this type of antibody response in normal individuals.

In its fifth year, the HIV Vaccine Trials Network (HVTN) continued to make improvements towards its operations and comprehensive goals. These include (1) streamlining protocol development to shorten the time needed to initiate new studies; (2) strengthening the

HVTN Clinical Coordinators Working Group, which assists and prepares new units for clinical research; (3) developing analytical criteria to evaluate the suitability of budgets submitted by units; (4) promoting junior investigators for leadership roles through selection to chair/cochair positions on protocols or HVTN committees; (5) continued strengthening of laboratory programs through expansion of proficiency testing and assay validation; (6) conducting more trials at participating international sites than in previous years; and (7) helping international sites develop plans for access to antiretroviral therapy for volunteers who acquire HIV infection during trial participation.

NIAID scientists at the VRC examined the breadth of T cell repertoire, i.e., the number of different T cells that make up the response to the AIDS virus. These researchers showed that T cell responses that are narrow in their repertoire cannot tolerate viral mutations and allow the virus to escape rapidly. Conversely, T cell responses that have a broad repertoire are likely more able to tolerate mutations and thus can contain the virus more easily. These considerations are extremely important in helping to establish a framework on which to base rational design of HIV vaccines.

(See the “Vaccine Research and Development” section on page 138 for additional vaccine information.)

## Nonvaccine Prevention Research

To control the HIV/AIDS pandemic, new and more effective methods and strategies are needed to prevent HIV infection. Until a highly efficacious vaccine is developed, control of the pandemic will still require a combination of prevention approaches. NIAID’s HIV Prevention Trials Network (HPTN) develops and tests promising nonvaccine strategies to prevent the spread of HIV/AIDS, including:

- Drugs or vaccines that are practical and easy to use to prevent mother-to-child

transmission (MTCT) of HIV, including prevention of viral transmission during breastfeeding;

- Microbicides to prevent sexual transmission of HIV;
- Antiretroviral therapy (ART) that could reduce the spread of HIV from infected persons to their sexual partners;
- Measures to control other sexually transmitted diseases and thereby decrease the risk of co-infection with HIV;
- Interventions to reduce behavior that exposes people to HIV; and
- Interventions to curb the spread of HIV among those who use intravenous and non-injection drugs.

NIAID-funded research within the HPTN has led to important scientific advances that increase our understanding about the transmission of HIV. These findings provide a foundation for developing and testing innovative prevention strategies.

Notably, microbicide research funded by the Division of AIDS has shown that combination microbicides can result in what appears to be synergistic inhibition of virus transmission in monkeys. Additional studies using a chemically modified form of RANTES (PSC-RANTES) have successfully provided the first proof that disruption of the virus-co-receptor interaction can afford complete protection of monkeys vaginally exposed to simian-human immunodeficiency virus (SHIV). Prevention research involving topical microbicides is described in the “Sexually Transmitted Infections” section on page 126.

## Therapeutics

One of the primary goals of HIV/AIDS therapeutic research is to evaluate new treatments

and innovative treatment strategies for HIV/AIDS and HIV-associated complications and infections. As a result of HAART, the life expectancy of HIV-infected individuals has dramatically increased. As individuals live longer with HIV, there is a greater likelihood of the development of drug resistance, metabolic abnormalities, co-infections, and drug toxicities. Moreover, the immune system only partially recovers during HAART treatment. Thus, new therapies and ways to expand the clinical benefit of currently approved therapies are still urgently needed. NIAID’s therapeutics research programs support research to address these issues.

In addition to a comprehensive clinical research agenda in the United States, NIAID fosters the study of HIV and HIV-associated infections internationally, including research in resource-poor countries. Key issues to be addressed in these countries include therapeutic regimens suitable for resource-poor settings; when to start HIV therapy; how to monitor safety and efficacy with minimal laboratory resources; interactions of endemic infections and HIV; strategies to prevent and treat co-infections; and drug interactions, including the drugs used to treat endemic infections. Efforts are underway to provide training to healthcare workers in developing countries to improve the management and treatment of individuals infected with HIV, as well as training for U.S. researchers in the healthcare needs of resource-poor countries. This is being accomplished through a variety of mechanisms, including the expansion of existing clinical trials groups to collaborate with investigators in resource-poor countries, direct funding of investigator-initiated research through R01 awards, and the development of comprehensive HIV research centers through the Comprehensive International Program of Research on AIDS. Through the Small Business Innovation Research mechanism, NIAID continues to support many small businesses seeking to develop technologies for monitoring patients in resource-limited settings, where

standard technologies like CD4+ and viral-load testing might be unaffordable.

The majority of NIAID's therapeutic clinical research is conducted through the clinical trials networks, Adult AIDS Clinical Trials Group (ACTG), the Pediatric AIDS Clinical Trial Group, and the Terry Beirn Community Programs for Clinical Research on AIDS. These networks conduct, at any given time, over 100 clinical studies to address a full range of HIV and HIV-associated infections, and complications. In addition to studies to assess treatments and treatment strategies, the networks conduct research in the following areas: co-infections such as hepatitis C virus (HCV); tuberculosis (TB); metabolic complications of HIV and HAART; opportunistic infections; treatment of naïve patients; salvage therapy, women's health, and the prevention of MTCT of HIV.

Currently, NIAID is conducting a large international clinical trial (ACTG 5175) to evaluate the efficacy of protease inhibitors and non-nucleoside reverse transcriptase inhibitors containing therapy combinations for initial treatment of HIV-infected individuals from diverse areas of the world. ACTG 5175 has completed stage 1 enrollment of patients in the following international sites: Johannesburg and Durban, South Africa; Chiang Mai, Thailand; Lilongwe and Harare, Malawi; and Lima, Peru. In addition, NIAID continues to support two large multicenter studies, the Strategies for Management of Anti-Retroviral Therapy (SMART) study ([www.smart-trial.org](http://www.smart-trial.org)) and the Evaluation of Subcutaneous Proleukin in a Randomized Interventions (ESPRIT) study ([www.niaid.nih.gov/dir/labs/lir/hiv/esprit.htm](http://www.niaid.nih.gov/dir/labs/lir/hiv/esprit.htm)).

In addition to the primary treatment studies, NIAID also supports ongoing network studies to address the timing and selection of antiretroviral regimens in the setting of acute opportunistic infections and co-infections such as TB and HCV, as well as treatment strategies to prevent

and treat metabolic disorders. One such study is a phase II long-term maintenance therapy trial designed to study whether long-term maintenance with pegylated-interferon (PEG-IFN) reduces the rate of disease progression in subjects with HCV/HIV co-infection who did not respond to the standard treatment regimen of PEG-IFN plus ribavirin (ACTG 5178).

The Maintaining Options for Mothers Study is a prospective, randomized clinical trial to evaluate the effectiveness of three different antiretroviral regimens for the prevention of nevirapine (NVP) resistance after single-dose NVP has been administered during delivery. Another important study, Optimal Combined Therapy after NVP Exposure is a phase III trial that compares the response of two different classes of antiretroviral drugs in women who have received only a single dose of NVP (ACTG 5208, OCTANE).

NIAID also continues to evaluate new classes of antiretroviral compounds, including viral entry inhibitors, which show increasing promise in preclinical and clinical studies. Building on the success of the fusion inhibitor, Fuzeon, NIAID is conducting studies focused on developing an orally available drug that will fight HIV at the point of entry.

### **NIAID Intramural Research**

Although recent advances in the treatment and monitoring of HIV-1 infection have substantially diminished HIV-associated illness and mortality, the management of HIV-infected patients has become increasingly complex. Both the acute and long-term toxicities of the common antiretroviral medications are becoming better understood and continue to complicate the successful management of this condition. Alternative treatment strategies are clearly needed, both for patients with access to ART and for the much greater number of patients with little or no access to therapy. NIAID clinical research is addressing many issues and strategies to improve patient care, including:

- Optimal dosing of anti-retroviral drugs;
- Integration of immune-based therapies with ART;
- Development of a successful ART strategy that employs periodic treatment interruptions;
- Optimal use of immune-based therapies to decrease exposure to ART;
- Characterization of immune recovery in persons with advanced HIV infection and discontinuation of prophylaxis against opportunistic infections; and
- Management of ART in individuals with advanced infection.

Studies employing serial interruptions of HAART seek to determine whether periodic treatment interruptions might offer therapeutic equivalence to continuous therapy.

The potential to substantially reduce the amount of medication required to effectively treat HIV infection could have widespread implications for the global effort to contain and treat the disease in terms of financial cost, toxicity to patients, and adherence to therapeutic regimens. In addition, periodic interruptions in ART could offer insights into the pathogenesis of HIV infection, immune responses, and other factors important to an individual's ability to control HIV replication.

Another major area of NIAID intramural research focuses on characterizing the immunologic abnormalities associated with HIV infection, developing immunologic approaches to the therapy of patients with HIV infection, and utilizing these immune-based therapies as tools for obtaining additional insights into the

pathophysiologic mechanisms present in patients with HIV infection.

Specifically, this research aims to reverse the CD4+ cell decline associated with progressive HIV-1 infection through the use of subcutaneous administration of IL-2. A series of randomized phase I/II studies have established this as a feasible method for increasing the CD4+ count in patients with HIV infection. These studies were then extended to optimize the dosing regimens for maximal immunologic and virologic benefit while minimizing side effects. Cohorts of patients are being followed who have received IL-2 treatment for periods that now extend to almost 10 years. Collaborations with a large number of extramural colleagues, both in the United States and abroad, aim to determine whether the favorable effects of IL-2 therapy on CD4+ counts translate into a significant delay in the onset of AIDS-defining conditions and/or death in recipients of IL-2 plus ART versus patients on ART alone.

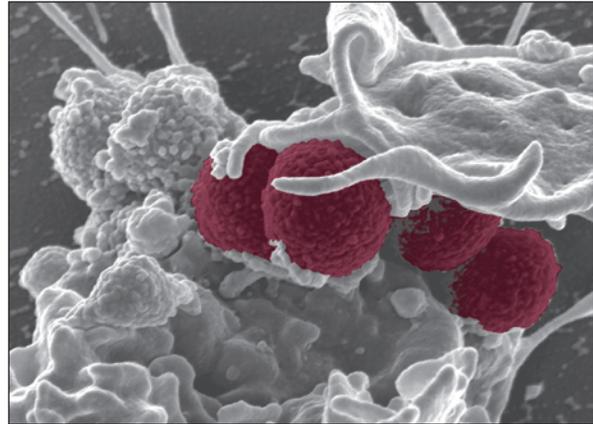
NIAID researchers have also performed phase I/II studies with a novel CCR5 inhibitor compound and are conducting phase II efforts to better characterize the activity, pharmacokinetics, and efficacy of this agent, both alone and when added to a conventional HAART regimen.

Efforts are continuing to improve access to clinical trials for local minority populations through an outreach program that includes a close relationship with local clinics for the medically underserved. Finally, NIAID researchers have played an active role in helping establish a clinical research infrastructure in the South African National Defense Force military healthcare system through participation in the HIV research projects organized under Project Phidisa.

## ANTIMICROBIAL RESISTANCE

Antimicrobial resistance has become an increasingly important public health problem because of the overuse of antimicrobial drugs and failure to ensure proper diagnosis and adherence to treatment. Drug-resistant infectious agents include those that are not killed or inhibited by antimicrobial compounds. Serious cases of resistance have occurred in hospitals and communities and include nosocomial (hospital-acquired) respiratory and bloodborne infections. Due to the emergence and spread of antimicrobial resistance, several bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus*, vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *Mycobacterium tuberculosis*, and penicillin-resistant *Streptococcus pneumoniae* are difficult to treat and have negative clinical outcomes. The impact of antimicrobial resistance includes an increase in the cost of treating infections, the need to use a greater number of broader spectrum and more toxic drugs to clear resistant infections, the development of untreatable infections leading to increased morbidity and mortality, and the spread of resistant infectious agents in hospitals and the outside community.

The phenomenon of antimicrobial resistance is prevalent in developed countries and also is a challenge for developing areas of the world. Factors in the global emergence of resistant malaria parasites, diarrheal pathogens, and sexually transmitted bacteria include incomplete or inadequate antimicrobial therapy, ineffective counterfeit drugs, and lack of access to health care. These factors are different from those that influence resistance patterns seen domestically. New prevention and treatment strategies are needed, as well as the effective use of the tools currently available for fighting resistant infectious diseases.



MRSA. Methicillin-resistant *Staphylococcus aureus*.

Hospitals are a critical component of the antimicrobial resistance problem. Many factors are believed to contribute to the emergence of drug resistance among nosocomial pathogens, including overuse of broad-spectrum agents, increasing numbers of susceptible and immunocompromised patients, use of invasive procedures and devices, and the breakdown of infection- and disease-control practices. Currently 5 to 10 percent of patients admitted to acute care hospitals acquire health care-associated infections, and the risks have increased steadily during the recent decades.<sup>4,5</sup> Approximately 2 million patients in the United States acquire an infection as a result of receiving health care in a hospital, and overall 70 percent of the bacteria causing such infections are resistant to at least one of the drugs most commonly used to treat these infections.<sup>6</sup>

Antimicrobial resistance negatively affects patient clinical outcome and cost to the healthcare system. Several studies utilizing different methodologies have concluded that MRSA infections are more frequently fatal than are methicillin-sensitive infections. One retrospective cohort analysis revealed a 22 percent difference between mortality in MRSA bacteremia (35.3 percent) compared with methicillin-sensitive bacteria (8.8 percent). Another study, which evaluated the health and economic impact of VRE infections, showed increases in case fatality

rates and hospital costs in the VRE group as compared to matched controls, respectively.<sup>7, 8, 9</sup>

One of the most disturbing trends is the emergence of multidrug-resistant pathogens in facilities other than hospitals. MRSA, long a problem in intensive care units (ICUs) and nursing homes, is an emerging community-acquired pathogen among patients without history of hospitalization or previous infections. There are increasing reports of MRSA causing serious skin and soft-tissue infections among athletes, prisoners, persons in daycare settings, and injection drug users.

*Streptococcus pneumoniae* (pneumococci) causes tens of thousands of cases of meningitis and pneumonia, and 7 million cases of ear infection in the United States each year. Multidrug-resistant pneumococci are common and increasing. Resistance of *S. pneumoniae* to antimicrobial agents continues to be a major public health concern.<sup>10</sup>

Group A streptococci (GAS, *Streptococcus pyogenes*) are the most frequent and important cause of bacterial pharyngitis in children and adults. Macrolide antibiotics are prescribed increasingly for treatment of pharyngitis due to GAS. A high prevalence of macrolide resistance has been recognized in Europe and Southeast Asia for many years. Recently, the emergence of erythromycin resistance in GAS in the United States, Canada, and Argentina has been reported.

Group B streptococci (GBS) remain a leading cause of serious neonatal infections resulting from the transfer of GBS from a colonized mother to her infant during labor and delivery. The number of GBS infections in infants has been reduced by intrapartum administration of antibiotics during labor, with penicillin as the agent of choice. However, recommended strategies for women who are allergic to penicillin have been updated to include cefazolin because of the increased

resistance to erythromycin and clindamycin and reports of cefoxitin resistance.<sup>11</sup>

An estimated 300 to 500 million people worldwide are newly infected with the parasites that cause malaria, and an estimated 1 million people die every year from this infection.<sup>12</sup> Resistance to chloroquine, once widely used and highly effective for preventing and treating malaria, has emerged in most parts of the world. Resistance to other antimalarial drugs also is widespread and growing.

Multidrug-resistant tuberculosis (MDR-TB) is as contagious as drug-susceptible tuberculosis but requires much more extensive and costly therapy. The incidence of MDR-TB has increased dramatically in the past decade, and strains of the tubercle bacillus that are resistant to one or more drugs are now present in all regions of the world.<sup>13</sup> Accurate and rapid diagnosis of MDR-TB often is not available, resulting in inadequate treatment of patients who, as a result, remain infectious longer and are able to spread MDR-TB to other persons. Because TB is a major cause of death in persons also co-infected with HIV, the spread of MDR-TB in this vulnerable population has the potential to dramatically increase the death toll from TB.

Diarrheal diseases cause an estimated 3 million deaths a year—mostly in developing countries where resistant strains of highly pathogenic bacteria, such as *Shigella dysenteriae*, *Salmonella typhimurium*, and *Vibrio cholerae*, are emerging. Eighty percent of *S. dysenteriae* isolates in Bangladesh, for example, have been found to be resistant to ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX), compared with approximately 40 percent of the other *Shigella* species.<sup>14</sup> Also, resistance is increasing to several critical antimicrobials used to treat invasive *Salmonella* infection, including extended-spectrum cephalosporins and quinolones. In resource-poor countries, drug-resistant *Salmonella* infections could eventually become untreatable.<sup>15</sup>

Finally, a study in Indonesia found *V. cholerae* O1 strains resistant to ampicillin, TMP-SMX, chloramphenicol, and tetracycline; similar results were obtained for non-O1 *V. cholerae* strains.<sup>16</sup>

In response to the increasingly important public health concerns outlined above, NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens. NIAID-funded projects include basic research into the disease-causing mechanisms of pathogens, host-pathogen interactions, and the molecular mechanisms responsible for drug resistance, as well as applied research to develop and evaluate new or improved products for disease diagnosis, intervention, and prevention.

In addition, NIAID supports clinical trial networks with the capacity to assess new antimicrobials and vaccines with relevance to drug-resistant infections. Among these networks are the AIDS Clinical Trials Group, the Collaborative Antiviral Study Group, the Tuberculosis Research Unit, the Vaccine and Treatment Evaluation Units, and the Bacteriology and Mycology Study Group, with one area of emphasis directed toward serious resistant bacterial infections. A study protocol, “Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units (STAR-ICU)” was initiated in FY 2005, and others are under development.

In recent years, NIAID has launched several projects to accelerate research on antimicrobial resistance, to develop products to address this challenge, and to support new clinical trial activities in this area. The Network on Antimicrobial Resistance in *Staphylococcus aureus* provides a repository of resistant bacteria, a registry of case information, and a network of investigators to support and stimulate research in the area of resistant bacterial infections. In FY 2002, NIAID announced an initiative called Partnerships for Novel Therapeutics and Vector-

Control Strategies in Infectious Diseases, with the goal of supporting partnerships to develop new drugs and diagnostics in areas that are not currently a high priority for industry but are likely to have a high impact on public health. In 2003, NIAID awarded 18 grants under a new initiative designed to encourage the submission of grant applications on “Innovative Approaches for Combating Antimicrobial Resistance.”

NIAID cochairs the Interagency Task Force on Antimicrobial Resistance with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration; eight other government agencies also are represented on the task force. In June 2005, a public meeting was held to discuss progress in implementing “A Public Health Action Plan to Combat Antimicrobial Resistance Part 1: Domestic Issues” and obtain feedback from stakeholders. The action plan, which was created in 1999, reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance, and is based on input from a wide variety of constituents and collaborators. The action plan is available online at CDC’s Antimicrobial/Antibiotic Resistance Web site, [www.cdc.gov/drugresistance](http://www.cdc.gov/drugresistance).

A research initiative, “Sepsis and CAP: Partnerships for Diagnostics Development,” was announced in August 2004. The purpose of this initiative is to support industry development of broad diagnostic technologies that provide early detection of select major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia. Nine awards were made. Also, a protocol for evaluating an anti-endotoxin vaccine for human use is in early phase studies. Preliminary results show that the anti-endotoxin vaccine appears to be safe and well-tolerated in humans. Studies to further evaluate safety, functional activity, and immunogenicity are underway.

NIAID also investigates antimicrobial resistance in its Division of Intramural Research (DIR). In laboratory and clinical studies, DIR scientists study the microbe and the host to elucidate factors contributing to resistance to a variety of antimicrobial drugs. For example, to respond to the growing threat to TB-control programs posed by the emergence of MDR-TB, DIR scientists are collaborating with colleagues from Yonsei University and National Masan Tuberculosis Hospital in Busan, South Korea, who established a center of excellence for the study of MDR-TB. The center is addressing the basic biology underlying the development of drug resistance and serving as a clinical site for a natural history clinical research protocol and for evaluation of novel anti-TB agents.

DIR scientists also are studying the contribution of biofilms—communities of microorganisms embedded in a mucoidal (slime) matrix—to drug resistance. A bacterium often associated with biofilms, *Staphylococcus epidermidis*, is the most common pathogen in hospital-acquired infections and is responsible for healthcare costs of more than \$1 billion per year. Although usually a harmless bacterium of human skin, *S. epidermidis* can cause septicemia or endocarditis in patients undergoing immunosuppressive therapy, in premature newborns, or in injection drug users. However, most infections occur after the insertion of indwelling devices such as catheters or prosthetic heart valves. In these cases, the ability of *S. epidermidis* to form biofilms is the most important virulence determinant. In a biofilm, the bacteria are dramatically less susceptible to antibiotic treatment and to attacks by human immune defenses. For these reasons, *S. epidermidis* infections are very difficult to eradicate. DIR scientists propose that drugs preventing and/or targeting biofilm formation will be of extraordinary use in antistaphylococcal therapy because they will enable the immune system to cope with an infection and increase

the efficiency of common antibiotics. To provide the scientific basis for the development of drugs interfering with biofilm formation, DIR scientists are investigating the molecular biology, biochemistry, and epidemiology of biofilm formation. This investigation includes studying specific factors contributing to biofilm formation, their regulation, and the interaction of biofilm-forming *S. epidermidis* strains with the host.

In 2005, DIR scientists found that a molecule called PGA (for poly-gamma-DL-glutamic acid) protects *S. epidermidis* from innate immune defenses, human antibiotic compounds, and salt concentrations similar to levels found on human skin. They used mice fitted with catheters to demonstrate that an *S. epidermidis* strain deficient of PGA was unable to cause infection while strains containing PGA did.<sup>17</sup> If a vaccine can be developed to negate the effect of the PGA, it could be useful against all pathogens in which PGA is a basis for disease development, such as *S. epidermidis* and *B. anthracis*, which causes anthrax.

DIR scientists investigating the molecular basis of community-acquired MRSA infections recently found that MRSA strains causing community infections in the United States are more virulent than an MRSA strain common in hospitals. Their work further suggested that enhanced community-acquired MRSA virulence is linked to (or results from) evasion of killing by neutrophils, which likely underlies the ability of prominent community-acquired MRSA strains to cause disease in individuals without known risk factors. The study also revealed potential vaccine antigens and targets for therapeutics designed to control *S. aureus* infections.<sup>18</sup>

NIAID will continue collaborating with industry in order to stimulate and augment research into antimicrobial resistance and continue the development of novel products to address resistant bacterial infections in healthcare settings.

## ASTHMA AND ALLERGIC DISEASES

Allergies are the result of inappropriate immune responses to normally harmless substances. Allergy symptoms vary widely, from the sneezing, watery eyes, and nasal congestion of mild “hay fever” to severe rashes, swelling, and shock. Asthma is a chronic inflammation of the lungs that airborne allergens can trigger in susceptible people; tobacco smoke, air pollution, viral respiratory infections, or strenuous exercise can also contribute. Asthma and allergic diseases can significantly decrease quality of life, employee productivity, and school attendance; in severe cases, they can be life-threatening. The goal of NIAID’s asthma and allergic diseases research program is to develop more effective treatments and prevention strategies.

Allergies are the sixth leading cause of chronic disease in the United States and cost the healthcare system \$18 billion annually.<sup>19</sup> About half of all Americans test positive for at least one of the 10 most common allergens (ragweed, Bermuda grass, rye grass, white oak, Russian thistle, *Alternaria* mold, cat, house dust mite, German cockroach, and peanut),<sup>20</sup> and about 50 million suffer from allergic diseases each year. Food allergy occurs in 6 to 8 percent of children aged six years or younger and in 2 percent of adults.<sup>21</sup> Common food allergens include cow’s milk, eggs, shellfish, and nuts; peanuts and tree nuts are the leading causes of fatal and near-fatal food allergy reactions.

The prevalence of asthma is also high. In 2005, 30 million people living in the United States had asthma, resulting in more than 480,000 hospitalizations and approximately 4,200 deaths. African Americans are disproportionately affected by asthma. In 2002, the asthma prevalence among non-Hispanic African Americans was approximately 30 percent higher than among non-Hispanic whites, and approximately double the level among Hispanics. Non-Hispanic African Americans had an asthma

attack prevalence about 30 percent higher than that of non-Hispanic whites, and almost 77 percent higher than Hispanics. Among individual race/ethnic groups, Puerto Ricans have the highest levels of asthma prevalence and asthma attack prevalence. For reasons that are still unclear, the prevalence of both allergy and asthma in the United States is increasing.

The causes, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases are major areas of emphasis for NIAID’s Division of Allergy, Immunology, and Transplantation. NIAID vigorously pursues research on asthma and allergic diseases by supporting investigator-initiated projects, cooperative clinical studies, a national network of research centers, and demonstration and education research projects.

In fiscal year (FY) 2005, NIAID established the Food Allergy Research Consortium, a collaborative research program designed to develop new approaches to treat and prevent food allergy. The consortium will conduct basic, clinical, and epidemiological studies, and develop educational programs aimed at parents, children, and healthcare providers. The program goals are to develop immune intervention strategies for preventing and treating food allergy; identify the mechanisms of development, loss, and re-emergence of oral tolerance; determine the molecular and functional characteristics of food allergens; and determine the role of the gastrointestinal tract in development and loss of oral tolerance. The consortium’s first project is a study of the development of and loss of tolerance to foods in a cohort of high-risk children. Its second project is a clinical trial to evaluate a potential therapy for peanut allergy.

The Inner-City Asthma Study, cofunded by NIAID and the National Institute of Environmental and Health Sciences (NIEHS), was a multicenter, randomized controlled trial that tested the effectiveness of two interventions in reducing asthma morbidity among inner-

city children with moderate to severe asthma. The study concluded in 2001. One intervention provided physicians with more detailed and up-to-date information on participants' recent asthma symptoms and medication use. The other intervention reduced exposure to environmental triggers such as tobacco smoke, allergens derived from cockroaches, house dust mite, mold, furry pets, and rodents. Participants were evaluated during both the 1-year intervention period and a 1-year followup period. The study included 937 children between the ages of 5–10 years, from seven inner cities. The environmental intervention decreased exposure to indoor allergens, including cockroach and house dust mite and tobacco smoke, resulting in reduced asthma associated morbidity.<sup>22</sup> The physician feedback letter resulted in no change in symptoms, but a 24 percent reduction in emergency room visits.<sup>23</sup>

One project within the Inner-City Asthma Study evaluated the impact of indoor and outdoor fine particles and co-pollutants on respiratory illnesses. Recently published data from this study, which was funded by NIAID, NIEHS, and the U.S. Environmental Protection Agency, demonstrate that approximately 25 percent of indoor particle concentration is contributed by outdoor particles. These data also show that smoking is the major source of indoor particles and that indoor concentrations of fine particles peak in the late evening in homes where smoking occurs, perhaps reflecting the influence of after-dinner smoking. Analysis of data pertaining to the effects of particle concentrations on asthma symptoms is currently underway.

The Inner-City Asthma Consortium (ICAC) is a NIAID-funded research network that evaluates the safety and efficacy of immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children, investigates the mechanisms of action of the immune-based therapies, develops and validates biomarkers of disease progression, and investigates the immunopathogenesis of asthma in inner-city

children. Current studies include an Asthma Control Evaluation, a randomized prospective study to evaluate the use of measurement of exhaled nitric oxide, which increases during periods of uncontrolled asthma, as a surrogate marker for asthma worsening; the Urban Environmental Factors and Childhood Asthma study, a longitudinal prospective study in inner-city children of the immunologic causes of the development of recurrent wheezing, including evaluation of cytokine response patterns; and the Inner-City Anti-IgE Therapy for Asthma trial, a randomized, double-blinded, placebo-controlled, parallel group, multicenter trial to evaluate the safety and efficacy of Xolair (omalizumab) in inner-city children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroids. The ICAC has completed an ancillary study, the German Cockroach Allergen Standardization Evaluation.

NIAID supports 13 Asthma and Allergic Diseases Research Centers (AADRCs), which are the cornerstone of the pathobiology component of the NIAID asthma and allergy research portfolio. The AADRCs conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases.

NIAID and the National Heart, Lung, and Blood Institute (NHLBI) cosponsor the Immune System Development and the Genesis of Asthma program, which supports research on changes in immune function that occur early in life and lead to the development of asthma. Identification of the cellular and molecular processes involved in the onset of asthma will provide the basis for devising novel and effective new immune-based strategies for asthma treatment and prevention that do not compromise the integrity of the immune system. NIAID supports seven research projects through this program and NHLBI supports six projects.

The Immune Tolerance Network (ITN) is an international consortium of basic scientists and clinical investigators that performs clinical research to evaluate the safety and efficacy of methods that can induce the immune system to tolerate certain antigens, including allergens, for the treatment of immune-mediated disorders. The ITN, which is co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International, has completed a trial of recombinant ragweed allergen-immunostimulatory DNA conjugates for the treatment of allergic rhinitis. Preliminary data suggest that this conjugate, when given to ragweed allergic patients prior to the ragweed season, reduced symptoms in both that year's and the following year's ragweed season. The ITN is conducting a trial to determine the efficacy of the combination of anti-IgE (omalizumab) and ragweed allergen immunotherapy for treatment of allergic rhinitis and is also developing three other allergy protocols. These include recombinant ragweed allergen-immunostimulatory DNA conjugates in asthma; asthma/allergy prevention in young children by oral mucosal immunotherapy with house dust mite, cat, and timothy grass; and peanut allergy prevention by oral administration, in infants, of bamba, a peanut butter snack.

More information on ITN is available at [www.immunetolerance.org](http://www.immunetolerance.org).

In FY 2004, NIAID established the Atopic Dermatitis and Vaccinia Network to develop short- and long-term approaches to reduce the incidence and severity of eczema vaccinatum, and protect individuals with atopic dermatitis from adverse consequences of vaccinia exposure.

An important NIAID intramural study is examining how allergen immunotherapy (AIT) reduces or prevents reactions to allergens such as pollen, dust, or cat dander. Although the efficacy of AIT in asthma is modest, it is nonetheless the only disease-modifying therapy for allergic asthma currently known. Certain types of white blood cells, called Th2 cells, produce substances that contribute to the development of allergies, while others, called Th1 cells, produce substances that can inhibit the development of allergies. This study will determine whether AIT changes the immune response to allergens by reducing the number of Th2 cells or by converting them into Th1 cells. A better understanding of the mechanisms underlying the clinical effectiveness of AIT might help scientists to discover new approaches to treating allergies and asthma.

## AUTOIMMUNE DISEASES

The immune system is essential to survival, and even a modest decrease in immune function can leave a person susceptible to infection. But the immune system itself can also *cause* disease, by inappropriately attacking the body's own organs, tissues, or cells.

More than 80 autoimmune diseases have been described to date. Some, such as type 1 diabetes, attack specific organs while others, such as systemic lupus erythematosus (SLE), involve multiple organs. Although many autoimmune diseases are rare, collectively they affect approximately 5 to 8 percent of the U.S. population. A disproportionate number of people with autoimmune disorders are women. For unknown reasons, the prevalence of autoimmune diseases is increasing.

NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic research studies provides the rationale for clinical strategies to diagnose autoimmune diseases and to develop novel treatments for ongoing disease.

In response to congressional interest in autoimmune diseases, NIH established the Autoimmune Diseases Coordinating Committee (ADCC) in 1998 to coordinate research on autoimmune disorders. Participation in this committee is very broad and includes the directors, or their designees, of each of the NIH Institutes and Centers involved in autoimmune disease research; representatives of other Federal agencies, including the Centers for Disease Control and Prevention and the Food and Drug Administration, whose programs include

health functions or responsibilities relevant to these diseases; and representatives from a number of private organizations concerned with autoimmune diseases.

As required by the Children's Health Act of 2000, ADCC prepared the Autoimmune Diseases Research Plan and presented it to Congress in late 2002. In March 2005, the ADCC submitted to Congress its third progress report, which summarized fiscal year (FY) 2003 NIH funding, research accomplishments, and programmatic activities in autoimmune diseases research. The report, "Progress in Autoimmune Diseases Research," is available to the public at <http://www.niaid.nih.gov/publications/pdf/ADCCFinal.pdf>.

In addition to its basic autoimmune research portfolio, DAIT supports several clinical research programs on autoimmune diseases. The Autoimmunity Centers of Excellence (ACEs) facilitate close interactions between clinicians and basic researchers to promote collaborative research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies; this program recently expanded from four to nine centers. Numerous ongoing ACEs-supported clinical trials include a phase I/II clinical trial of anti-CD20 for treatment for lupus, a phase I clinical trial of anti-tumor necrosis factor for treatment of lupus nephritis, and a preclinical study of DNase treatment now underway with a follow-on phase Ib trial planned.

The Autoimmune Disease Prevention Centers conduct research on the development of new prevention strategies for autoimmune diseases and evaluate these approaches in pilot and clinical studies. In FY 2005, the centers supported 22 pilot projects to test innovative prevention approaches or methods to measure biomarkers of autoimmune disease progression.

NIAID, in partnership with the National Institute of Diabetes and Digestive and Kidney

Diseases, and the Juvenile Diabetes Research Foundation International, cosponsors the Immune Tolerance Network (ITN). This international consortium of more than 80 scientists and physicians is dedicated to the discovery and evaluation of methods that can induce stable, long-term immune tolerance in patients with many immune-mediated disorders, including autoimmune disorders. Tolerance strategies attempt to reprogram immune cells so they no longer attack the patient's own tissues, but are still able to effectively guard the body against infection. Because tolerance-inducing therapies would eliminate the need for lifelong immunosuppressive drug regimens—which themselves have serious side effects—they have the potential to revolutionize the management of many autoimmune diseases. The network has established several state-of-the-art core facilities and has supported 18 approved clinical protocols, as well as several additional studies of the immune mechanisms involved in tolerance. More information on ITN is available at [www.immunetolerance.org](http://www.immunetolerance.org).

Through the Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases, NIAID developed clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat severe autoimmune diseases such as multiple sclerosis, SLE, and scleroderma. Studies of the underlying immune mechanisms of autoimmune diseases will be performed along with the clinical trials. More information about NIH clinical research studies is available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). These complex trials are expected to open in FY 2006. The consortium will also conduct studies of the underlying immune mechanisms of these diseases and treatments as the trials progress.

DAIT supports three genetics research resources for autoimmune diseases. The Multiple Autoimmune Disease Genetics Consortium collects clinical data and genetic material from families in which at least two individuals have two or more autoimmune diseases. The

data and samples will be made available to researchers studying the genetics of susceptibility or resistance to autoimmune diseases. More information can be found at [www.madgc.org](http://www.madgc.org).

The North American Rheumatoid Arthritis Consortium (NARAC) collects clinical data and genetic material from families with rheumatoid arthritis. These data are made available to investigators to facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis. NARAC is jointly supported by DAIT, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Arthritis Foundation. More information can be found at [www.naracdata.org](http://www.naracdata.org).

In FY 2005, NIAID, with co-sponsorship from NINDS, awarded five research cooperative agreements under the new program, Human Leukocyte Antigen (HLA) Region Genetics in Immune-Mediated Diseases. The objectives of this program are to define the association between HLA region genes or genetic markers and immune-mediated diseases, including risk and severity of disease and organ and cell transplantation outcomes. This program is the successor to the International Histocompatibility Working Group (IHWG). More information about the IHWG can be found at <http://www.ihwg.org>.

Although researchers have made considerable progress in understanding the immune mechanisms that mediate tissue injury in autoimmune diseases, much remains to be learned. In particular, scientists are studying the causes of these diseases, the genetic factors that make people susceptible to them, and the regulatory mechanisms that control autoantibody production. NIAID is committed to advancing the understanding of how and why autoimmune diseases occur, and to promoting the application of basic research to clinical investigations in order to develop more effective therapeutic approaches and prevention strategies.

## BIODEFENSE

Recent world events have raised awareness of both the possibility of a bioterrorist attack and the vulnerability of the U.S. population to such an event. In fact, a terrorist attack on the United States using biological agents occurred in the fall of 2001, when *Bacillus anthracis* spores were sent through the U. S. mail, causing 18 confirmed cases of anthrax (11 inhalation, 7 cutaneous). In 2003 and 2004, ricin was found in an envelope at a postal facility in South Carolina and a Senate Office Building in Washington, D.C., and was used to contaminate several jars of baby food in California. Although the Department of Defense has developed countermeasures against biological warfare, there are additional concerns that need to be addressed to provide an adequate civilian defense from a bioterrorist attack. The number of microbial pathogens that threaten civilian populations is larger than that of classical biological warfare threats. Moreover, the populations to be protected are different because civilians include people of all ages and physical conditions.

In 2002, NIAID developed a strategic plan for biodefense research that outlines plans for addressing research needs for bioterrorism and emerging and re-emerging infectious diseases. In addition, NIAID convened a Blue Ribbon Panel of experts to provide objective scientific advice on NIAID's biodefense research agenda on so-called Category A agents. This list, which is defined by the Centers for Disease Control and Prevention (CDC), includes the most dangerous threat agents, such as smallpox and anthrax. The expert panel was asked to assess the current research, identify goals for the highest-priority areas, and make recommendations to achieve the goals. In the fall of 2002, NIAID convened a similar expert panel to assess current research and identify goals for Category B and C agents. In the areas of immunology and biodefense, NIAID has convened two more advisory bodies: an Expert Panel on Immunity and Biodefense,

to assess future immunology research most important to combat bioterrorism and emerging infectious diseases; and an Expert Panel on Atopic Dermatitis and Vaccinia Immunization, to develop a research plan to reduce the risk of eczema vaccinatum, a serious and sometimes deadly complication of smallpox immunization in atopic dermatitis patients.

In the past year, NIAID has continued to expand, intensify, and accelerate its ongoing research programs in biodefense. NIAID has launched research initiatives in areas ranging from the basic biology of microbes and their interactions with the human immune system to preclinical and clinical evaluation of new therapeutics and vaccines. These initiatives are designed to take advantage of the recent outpouring of ideas from academic and industrial scientists on ways to understand and combat potential agents of bioterrorism ([www3.niaid.nih.gov/biodefense](http://www3.niaid.nih.gov/biodefense)).

In FY 2005, NIAID made its first grant and contract awards using authorities granted by the Project BioShield Act of 2004 to expedite



**Ebola Virus.** Scanning electron micrograph of Ebola virus, which causes hemorrhagic fever and is designated a Category A agent.

research and development on critical biomedical countermeasures, including countermeasures for Category A agents. In addition, NIAID released two progress reports highlighting accomplishments in biodefense research during the 18 months subsequent to the development of the strategic plan ([www.niaid.nih.gov/biodefense/research/category\\_a\\_progress\\_report.pdf](http://www.niaid.nih.gov/biodefense/research/category_a_progress_report.pdf); [www.niaid.nih.gov/biodefense/research/category\\_bc\\_progress\\_report.pdf](http://www.niaid.nih.gov/biodefense/research/category_bc_progress_report.pdf)).

## Basic Research

One of the most important basic research tools that has evolved in recent years is the ability to rapidly sequence the entire genomes of microbial pathogens, including potential agents of bioterrorism. This capability allows scientists to identify microbial genes that play a role in disease and then design drugs that can block the activities of the proteins encoded by these genes. NIAID has made a significant investment in the DNA sequencing of the genomes of microorganisms considered agents of bioterrorism, including several Category A, B, and C agents. Organisms NIAID has helped to sequence include *Brucella suis*, *Burkholderia mallei*, *Clostridium perfringens*, *Coxiella burnetii*, *Rickettsia typhi*, *Staphylococcus aureus*, *Yersinia pestis*, *Mycobacterium tuberculosis*, *Vibrio cholerae*, *Cryptosporidium parvum*, *Giardia lamblia*, *Entamoeba histolytica*, *Toxoplasma gondii*, diarrheagenic *Escherichia coli*, *Shigella*, and *Salmonella*. In addition, NIAID has expanded its sequencing efforts of *B. anthracis* beyond the Ames strain used in the 2001 attack and has developed a comprehensive genomic analysis that includes sequencing several additional strains, clinical isolates, near neighbors, and related species. These sequences will facilitate forensic strain identification; understanding of microbial pathogenesis; discovery of new targets for drugs, vaccines, and molecular signatures; and discovery of biomarkers for diagnostics to combat bioterrorism.

To expand its current enteric pathogens research network, NIAID established the Food and Waterborne Diseases Integrated Research Network to include multidisciplinary research on all food- and waterborne pathogens or toxins. The network facilitates the development and evaluation of products to rapidly identify, prevent, and treat food- and waterborne diseases that threaten public health.

NIAID funds the Centers for Medical Countermeasures against Radiation, which will focus on basic and applied research to develop new products for measuring radiation exposure, protect against exposure, and minimize and treat the effects of exposure to a wide range of radioactive compounds.

## Immunity and Biodefense

Considerable knowledge about the mechanisms of host immune responses to microbial pathogens has been gained in recent years. Studies of innate immune mechanisms, which serve as a nonspecific first line of defense against pathogenic infection, have been especially productive. In FY 2004 and 2005 several of the contracts awarded under the Immune Epitope Discovery Program made significant progress in the identification of antibody and T cell epitopes to such pathogens as influenza, vaccinia virus, and *Clostridium botulinum* neurotoxins. Finally, the threat of bioterrorism and the natural emergence of diseases due to microbes such as West Nile virus (WNV) and severe acute respiratory syndrome (SARS) virus underscore the importance of defining the immune parameters responsible for increased susceptibility to infectious diseases of infants, young children, the elderly, and immunocompromised individuals.

To gain a better understanding of the human immune response to potential agents of bioterror, NIAID funded eight Cooperative Centers for Translational Research on Human Immunology and Biodefense. These centers, located throughout the country, focus on the rapid development of

bioterrorism countermeasures, such as vaccines and therapies.

Also contributing to the biodefense vaccine effort are a number of recent contracts awarded to identify immune epitopes for Category A, B, and C pathogens; define human genetic variance that contributes to infection susceptibility or vaccine efficacy; identify new candidates for vaccine adjuvants; develop reagents for nonhuman primate studies of new drug or vaccine candidates; and address the problem of eczema vaccinatum as a serious adverse consequence of the current smallpox vaccine.

### New Diagnostic Tools

NIAID also supports research leading to the development of new and improved diagnostics. The goals of this research are to establish methods for the rapid, sensitive, and specific identification of natural and bioengineered microbes, as well as to determine the microbes' sensitivity to drug therapy. Progress in these areas will allow healthcare workers to diagnose and treat patients more accurately and quickly.

NIAID continues to support initiatives specifically for the development of the next generation of medical diagnostics, and also continues to support its Small Business Biodefense Program, which encourages the development of therapeutics, vaccines, adjuvants and other immunostimulants, diagnostics, and selected resources for biodefense by the small business research community. This program expands the duration and dollar limits for small business grants to develop specified products that are considered high priority for biodefense.

NIAID supports a range of biodefense genomics research projects that provide comprehensive genomic, bioinformatics, functional genomics, and proteomic research resources to the scientific community to help researchers identify targets and proteins for use in new diagnostics. Through these projects, NIAID awarded contracts in

FY 2004 for eight Bioinformatics Resource Centers to develop and maintain comprehensive, relational databases for genomic and related data for microorganisms responsible for emerging and re-emerging infectious diseases and for those considered agents of bioterrorism ([www.niaid.nih.gov/dmid/genomes/brc/default.htm](http://www.niaid.nih.gov/dmid/genomes/brc/default.htm)).

In FY 2005, NIAID continued to support contracts for the Biodefense Proteomics Research Centers to develop and enhance innovative proteomic technologies and apply them to the understanding of the pathogen and/or host cell proteome for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics, and immunotherapeutics against microorganisms considered agents of bioterrorism. NIAID funds seven centers that are working on a range of proteomics studies including agents from Categories A, B, and C.

### Vaccines

NIH-supported researchers are developing vaccines against many infectious agents, including those considered to be bioterrorism threats, for use in civilian populations of varying ages and health status. Vaccines are being developed using both traditional and novel technologies. Significant progress has been made in the development of next-generation vaccines for anthrax and smallpox, and in the development of new vaccines for other diseases such as Venezuelan equine encephalitis (VEE), West Nile virus, plague, and cholera. Ongoing modified vaccinia Ankara (MVA) and recombinant protective antigen contracts for smallpox and anthrax vaccines, respectively, continue to support scaled manufacturing of the vaccines, as well as further safety testing in humans and safety and efficacy studies in animals. In 2005, NIAID awarded three contracts to fund development of new vaccines against tularemia and botulinum. The tularemia and botulinum contract awards will fund early-stage product development of the respective vaccines, including dosage formulation,

pilot batch production, and initial clinical assessment.

## Therapeutics

NIH therapeutics research focuses on the development of new antimicrobials and antitoxins, as well as the screening of existing antimicrobial agents to determine whether they have activity against organisms that might be used by bioterrorists. Knowledge gained from basic and applied research is helping to identify additional targets for medications and immune-based therapies against agents of bioterrorism.

Through the *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program, NIAID continues to provide a range of resources for preclinical testing of new therapies and vaccines, including nonhuman primate models. Under these contracts, small animal and nonhuman primate models will be developed and validated for licensure of vaccines and therapeutics by the U.S. Food and Drug Administration (FDA).

Also, through the *In vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program, NIAID is screening existing FDA-approved antimicrobials for efficacy against inhalational anthrax. Through its *in vitro* antiviral screening contracts, NIAID has supported the evaluation of compounds for *in vitro* activity against models for NIAID biodefense Category A, B, and C viruses, such as influenza, yellow fever, dengue, West Nile virus, VEE, Pichinde virus (a surrogate for arenaviruses), and Punta Toro virus (a surrogate for Rift Valley fever, sandfly fever, and hantavirus). Approximately 1,600 compounds were screened in FY 2005.

The NIAID *in vivo* antiviral screening contracts support the evaluation of many compounds against NIAID Biodefense Category A, B, and C viruses or their surrogates such as influenza, orthopoxviruses (including surrogates for smallpox), Punta Toro virus, Pichinde, SARS

coronavirus (CoV), Banzi (a surrogate for yellow fever), Venezuelan equine encephalitis, and West Nile virus.

Grants awarded for Accelerated Product Development for Radiation Countermeasures will support projects focused on protecting the immune system from radiation or restoring the immune system following radiation exposure.

Contracts for the Development of Radiation Countermeasures were awarded to evaluate promising compounds to prevent, reduce, or treat symptoms of radiation exposure. Additionally, three contracts were awarded for Development of Improved DTPA (diethylenetriaminepentaacetate) for Radionuclide Chelation. DTPA can be used to remove certain radioactive compounds from the body. If an individual is exposed to one of these compounds, DTPA can be given intravenously to help eliminate the contamination. For use following a terrorist attack, however, DTPA would be practical only in an easier-to-administer form. These contracts will seek to develop alternate ways to effectively administer DTPA, either by inhalation, oral liquid, or pill.

NIAID also has expanded the Collaborative Antiviral Study Group (CASG) by approximately 20 percent since it was established in 1986. In 2003, CASG developed a clinical protocol for the treatment of smallpox with cidofovir, in the event of an outbreak or release. NIAID will soon be supporting a phase I clinical study by Chimerix, Inc., to assess initial safety, tolerability, and pharmacokinetics of a promising new oral derivative of cidofovir in normal volunteers. The CASG will conduct future phase I/II studies with the drug after the initial phase I study is complete. The CASG is also conducting a phase I/II study on the safety and tolerability of an immune globulin treatment for West Nile virus neuroinvasive disease and is conducting a natural history study of the clinical outcomes of WNV neuroinvasive disease. In addition, the CASG

is initiating a chart review study of the use of oseltamivir in young children less than 2 years of age with confirmed or suspected influenza. The FDA recently cleared ST-246, a smallpox antiviral developed by SIGA Technologies, Inc., for a phase I clinical trial that will be supported by NIAID and conducted at the NIH Clinical Center. This trial is awaiting Institute review board approval and is slated to begin March 2006.

NIAID also funds research focused on the discovery and development of botulism therapeutics that would be effective in a post-exposure scenario.

## Research Resources

NIAID continues to support the expansion of centralized laboratory resources, including regional biosafety laboratories, *in vivo* and animal model resources, drug-screening contracts, the production of standardized and validated reagents and tests, and genomic and bioinformatics resources. The availability of such resources assists the research community in conducting studies of biodefense pathogens.

In FY 2005, NIAID completed a national network of 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), to support research focused on countering threats from bioterror agents and emerging infectious diseases. Each center is comprised of a consortium of universities and complementary research institutions serving a specific geographical region. The primary objective of the RCE program is to support the NIAID biodefense and emerging infectious diseases research agenda. The RCEs, located throughout the United States, will build and maintain a strong scientific infrastructure supporting multifaceted research and development activities that promote scientific discovery and translational research capacity required to create the next generation of therapeutics, vaccines, and diagnostics for the NIAID Category A, B, and C agents. The

research being conducted within the RCEs spans a broad range of biodefense and emerging infectious disease topics including:

- Basic research on bacterial and viral disease processes;
- New approaches to blocking the action of anthrax, botulinum, and cholera toxins;
- Developing new vaccines against anthrax, plague, tularemia, smallpox, and hemorrhagic fevers;
- Creating new immunization strategies and delivery systems;
- Generating new antibiotics and other therapeutics;
- Designing new advanced diagnostic methods and devices;
- Conducting immunological studies of host-pathogen interactions; and
- Developing computational and genomic approaches for studying infectious diseases.

In 2005, NIAID enlarged its network of National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs) by awarding grants to fund the construction of 4 more RBLs, for a total of 2 NBLs and 13 RBLs. The NBLs will serve as national and regional resources for research on biodefense and emerging infectious disease agents that require biosafety level (BSL) -4/3/2 biocontainment, and the RBLs will serve as regional resources for research requiring BSL-3/2 biocontainment. These laboratory facilities will be designed and built using the strictest federal standards, and will incorporate multiple layers of safety and security to protect laboratory workers and the surrounding environment.

The NBLs and RBLs will complement and support the research activities of NIAID's RCEs.

The biosafety labs also will be available and prepared to assist national, State, and local public health efforts in the event of a bioterrorism or infectious disease emergency.

NIAID established the Biodefense and Emerging Infections Research Resources Repository in September 2003 to provide unique and quality-assured biodefense-related reagents and resources to the scientific community for basic research and product development. This program facilitates the understanding of the pathogenesis of NIAID Category A, B, and C priority pathogens and emerging infectious diseases organisms and toxins and aids in the development and evaluation of vaccines, therapeutics, and diagnostics for these organisms and agents. The repository also assists with access to reagents not held in the program.

In order to facilitate research and product development for biodefense and emerging infectious diseases, the repository collects information about biodefense-related reagents and standards and disseminates this information through print, electronic media, and workshops; enhances technology transfer through development and publication of methods; and facilitates commercial development of reagents through proactive communication with biotechnology and pharmaceutical companies. In addition to securing acquisition, storage, and the distribution of biological agents and toxins, the repository generates new reagents as scientific advances are made.

It is anticipated that in the long-term the Biodefense and Emerging Infections Research Resources Repository will become a national resource and clearinghouse for biological organisms and toxins, reagents, and information on these organisms. By centralizing this function, access to and use of these materials can be monitored and quality control of the reagents assured. Information about this resource is now available on the Web site at [www.beiresources.org](http://www.beiresources.org).

For more information on the numerous NIAID resources available to biodefense researchers, visit [www2.niaid.nih.gov/biodefense/research/resources.htm](http://www2.niaid.nih.gov/biodefense/research/resources.htm).

## NIAID Intramural Research Programs

### **Basic Research Discoveries**

The NIAID Division of Intramural Research (DIR) studies of *B. anthracis*, the bacterium that causes anthrax, are focused on the identification, genetic regulation, and analysis of anthrax lethal toxin and other virulence factors, as well as the development of improved vaccines and therapeutics. The anthrax toxin is the primary cause of damage to animal tissues during an anthrax infection. DIR scientists are studying the action of the toxin in appropriate small animal models to identify molecular targets of anthrax toxin and opportunities for specific therapy of anthrax infections. Recent studies to determine why mice strains differ greatly in susceptibility to anthrax lethal toxin revealed that steroid therapy increased their sensitivity to the toxin.<sup>24</sup> This result suggests that steroid therapy for anthrax could have potentially detrimental consequences that should be considered in treatment protocols for this disease.

In addition, NIAID intramural anthrax research has promising nonbiodefense applications. For example, new knowledge about anthrax toxin structure and function is also being used to create toxin-based therapeutic agents targeted specifically to cancer cells. These toxins have shown efficacy in mouse tumor models and are being developed by a licensee for possible clinical application.

DIR investigations of *Yersinia pestis*, the bacterium that causes plague, have resulted in the development of both mouse and rat models of bubonic plague that incorporate the natural flea-borne route of transmission. The mouse model has been used to test two plague vaccine

candidates. The first, developed by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) was recently found to be 100 percent effective in mice. The second, a new live-attenuated vaccine for plague, remains under investigation.

The plague investigators also characterized the Brown Norway rat as a small animal model in which to study *Y. pestis* transmission and pathogenesis and the host response to plague. The development of the gross pathology and histopathology in the bubo, or infected lymph node, was characterized and shown to closely resemble human bubonic plague. Characterization of the disease and host response in this small animal model enables discoveries that could help scientists develop improved therapies and vaccines.<sup>25</sup> This work is important to NIAID's biodefense efforts as well as to efforts to control naturally occurring plague epidemics.

To better understand the innate immune response, DIR scientists are studying infection-fighting white blood cells called neutrophils, which are an essential part of human innate immunity. In 2005, NIAID researchers completed microarray studies of human neutrophil polymorphonuclear leukocyte function and are pursuing research to elucidate the role of selected genes and proteins identified in these studies. By describing changes in neutrophil gene expression in response to bacterial invasion, the investigators have identified dozens of possible targets for drug therapies. These findings are likely to be broadly applicable to many types of microorganisms that cause disease in humans and could lead to new treatments that augment the immune response against multiple high-priority pathogens.<sup>26</sup>

Additional investigations underway in NIAID laboratories include studies of the pathogenesis of *C. burnetii*, the agent of Q fever; studies of multidrug-resistant tuberculosis; studies of relapsing fever agents with a focus on improving diagnostic tests; and a new program to identify

and characterize antigens suitable for use in a vaccine against *Burkholderia mallei* and *Burkholderia pseudomallei*, the causative agents of glanders and melioidosis, respectively; and a new tularemia research program. The tularemia-causing agent, *Francisella tularensis*, is a highly infectious bacterium whose virulence is enhanced by its ability to survive and replicate within host cells called macrophages—normally strong defenders against bacterial infection. The new program focuses on understanding how the bacterium survives inside the macrophages of the host in order to uncover novel targets for the design of vaccines and therapeutics against tularemia. This research is supported by enhanced genomics and proteomics capabilities on the Bethesda campus and at the Rocky Mountain labs.

The molecular events that underlie Ebola virus cytopathicity are poorly understood. Scientists at the NIAID Vaccine Research Center (VRC) have identified a cellular mechanism responsible for Ebola glycoprotein (GP) cytotoxicity. Through its effects on specific cell-surface molecules, Ebola virus disrupts several processes essential for immune activation and recognition, such as cell trafficking and antigen presentation. By altering the trafficking of select cellular proteins, Ebola GP inflicts cell damage and can facilitate immune escape by the virus. This mechanism is likely responsible for the inflammatory dysregulation, immune suppression, and vascular dysfunction that are hallmarks of lethal Ebola virus infection. These findings are important for developing countermeasures against the pathogenic effects of the virus.

### Vaccines

NIAID has a longstanding intramural research program aimed at shedding light on the molecular biology and gene expression mechanisms used by vaccinia—the virus used in the current smallpox vaccine—and other poxviruses. A primary aim of this program is the development of MVA as a carrier for the delivery of vaccine components and gene therapies to

target cells. Intramural poxvirus researchers, who have decades of experience with MVA, and other poxvirus scientists are collaborating with USAMRIID researchers and others in nonhuman primate studies of MVA's efficacy as a smallpox vaccine. In a study comparing MVA and Dryvax (the traditional licensed smallpox vaccine) in a monkey model, scientists found that after two doses of MVA or one MVA dose followed by Dryvax, the immune response was equivalent or higher than that induced by Dryvax alone. After challenge with monkeypox virus, unimmunized animals developed hundreds of skin lesions and became gravely ill or died, whereas vaccinated animals were healthy and asymptomatic, except for a small number of transient skin lesions in animals immunized only with MVA. Their findings were important steps in the evaluation of MVA as a replacement vaccine or pre-vaccine for those with increased risk of severe side effects from Dryvax.<sup>27</sup>

In addition, the VRC completed two clinical trials to evaluate the safety and immunogenicity of MVA. One study involved young adults who had never been vaccinated against smallpox; the other was designed for older adults who had been vaccinated more than 10 years ago. The vaccine was provided by Therion Biologics Corporation as part of a collaboration with the VRC. MVA is an attenuated strain of vaccinia virus that is replication-defective, and therefore does not cause a lesion at the site of inoculation typical of Dryvax. MVA had fewer side effects than Dryvax and was found to be well tolerated and immunogenic. MVA given prior to Dryvax reduced Dryvax-related side effects and improved immunogenicity.

NIAID DIR scientists also continued basic investigations to determine if pieces, or subunits, of the vaccinia virus could be used to make a protective vaccine against smallpox. Such a vaccine would likely have fewer side effects than the current vaccine. Toward this goal, they found that a vaccine made from three recombinant

proteins of the outer membranes of intracellular and extracellular virus protected mice from 10 times the usual lethal dose of the Walter Reed vaccinia strain. The results of these studies suggest that an effective smallpox vaccine could be made from subunits of vaccinia.

Hemorrhagic fevers such as those caused by Ebola virus are associated with a high mortality rate, particularly for the Ebola Zaire subtype. Traditional public health measures to prevent future outbreaks are limited, thus increasing the urgency for development of an effective vaccine. An interagency agreement currently in place between NIAID and USAMRIID allows for collaboration in animal studies, assay performance, and data analysis.

Investigators at the VRC, with scientific collaborators at USAMRIID and the CDC, have developed a potentially effective vaccine strategy for Ebola virus infection in nonhuman primates. In November 2003, the VRC initiated the first human clinical trial of a DNA vaccine designed to prevent Ebola infection. The vaccine was well tolerated and there is evidence of both humoral and cellular immune responses at all dose levels. The VRC also has plans to evaluate a fast-acting, recombinant adenoviral vector Ebola vaccine. Such a vaccine would be especially useful in an acute outbreak setting. If this vaccine proves to be effective in humans, it could one day be used to quickly contain Ebola outbreaks with the same ring vaccination strategy used in the past against smallpox. This product is currently in the preclinical testing phase and a phase I study is projected to begin in summer 2006.

The VRC also is developing vaccines against West Nile virus and SARS. For West Nile virus, the VRC's candidate vaccine is based on an existing codon-modified, gene-based DNA plasmid vaccine platform designed to express WNV proteins. In April 2005, following preclinical safety studies and viral challenge studies, the VRC initiated a phase I clinical trial to evaluate the safety, tolerability, and immune responses of this

recombinant DNA vaccine in human volunteers. Also in collaboration with Vical, Inc., the VRC is currently developing a second-generation DNA vaccine using an improved expression vector expressing the same WNV proteins. A phase I clinical trial is planned for spring 2006.

In response to the recent global outbreak of SARS, VRC investigators began work immediately on the development of a potential vaccine. The VRC contracted with Vical, Inc., to manufacture a single closed, circular DNA plasmid-based vaccine encoding the S protein of SARS-CoV. VRC studies using mice as an experimental model demonstrated that this vaccine induces T cell and neutralizing antibody responses, as well as protective immunity. A phase I open-label clinical study to evaluate safety, tolerability, and immune response was initiated in FY 2005, fully enrolled volunteers, and is now closed to accrual.

### **Therapeutics**

NIAID clinical investigators have an approved protocol in place that will allow them to evaluate and treat persons exposed to or infected with anthrax, and to conduct immunologic evaluations of recipients of anthrax vaccines. In addition, DIR investigators and their colleagues in the NIH Clinical Center are collecting serial blood samples and throat swabs from healthy persons who receive the smallpox vaccine in order to measure serum cytokines and look for the smallpox vaccine virus. Identification of specific cytokines induced after vaccination could help to explain certain side effects associated with the smallpox vaccine and suggest new ways to modify some of these side effects. The investigators also evaluated different methods of detecting the smallpox vaccine virus in clinical specimens, including sensitive cell culture methods, polymerase chain reaction studies, and a direct fluorescent antibody test that detects viral proteins. These studies indicated which test detects the virus most reliably, which is the fastest to perform, and which tests give false-positive results for other viruses.

DIR poxvirus researchers also identified three poxvirus proteins that are required for virus entry and fusion with the cell. Remarkably, these proteins are conserved in all poxviruses analyzed to date, indicating that the mechanism of poxvirus entry into cells is also conserved. The identification of the entry proteins is crucial for understanding how poxviruses spread and cause disease. In addition, these proteins are potential targets for poxvirus therapeutics.

Protective antibodies are produced by the host in response to infection or immunization. Administration of sera containing protective antibodies to people exposed to a pathogen is called passive immunoprophylaxis and has long been used to prevent disease in exposed populations. However, monoclonal immunoglobulin preparations tailored to act specifically on the most vulnerable parts of an invading pathogen could be of higher and more consistent potency.

DIR researchers are pursuing several prophylaxis and treatment strategies based on monoclonal antibodies, including the development of preparations that can be used to prevent or treat complications of smallpox vaccination, smallpox, anthrax, SARS, West Nile virus, botulism, rabies virus, Japanese encephalitis virus, and the tick-borne encephalitis virus complex. For example, DIR researchers derived monoclonal antibodies from chimpanzees—which are virtually identical to human antibodies—that can neutralize the protective antigen toxin of *Bacillus anthracis*, and tested them in both cell culture and in a rat model. These monoclonal antibodies attached to the anthrax toxin with greater strength than any previously developed anthrax antibodies, and they protected rats from death following infusion of anthrax toxin. The results of these studies are very encouraging for the development of a monoclonal-based immunotherapy to neutralize the effects of anthrax toxin in infected or exposed humans.

**Resources**

In FY 2005, the Vaccine Research Center established the Biodefense Research Section, a new laboratory within the Center focusing on three major areas: (1) development of vaccines and antivirals against hemorrhagic fever viruses

such as Ebola, Marburg, and Lassa; (2) studies of the mechanism of vaccine-induced immune protection; and (3) basic research to understand the mechanism of virus replication (entry) and neutralization.

## BIOENGINEERING, BIOINFORMATICS, AND ADVANCED TECHNOLOGIES

Bioengineering, bioinformatics, and other advanced technologies provide crosscutting tools that facilitate research in many disciplines. Bioengineering combines physics, chemistry, and mathematics, as well as basic engineering principles to enhance the study of biology, medicine, behavior, and health. Bioinformatics and computational biology apply computer science and advanced mathematics to the fields of biology and medicine to enable integration and analyses of biological, medical, behavioral, and health data. Other advanced technologies, such as biomedical imaging, proteomics, and genomics, facilitate the characterization of complex biological processes.

The powerful tools and techniques of bioengineering, bioinformatics, and computational biology extend the capacity of science to perceive, capture, and manage information about biological processes. They have become integral components of NIAID-supported basic and clinical infectious diseases and immunology research. Additional technologies, including genomics, proteomics, biosensor fabrication, biomedical imaging, and data integration, also are becoming important tools for researchers. Below are examples of NIAID-supported programs in these areas.

- **Mass spectrometry for high-throughput peptide characterization.** This program supports the development of chemical measurement instruments for the sequence analysis of peptide antigens presented in the major histocompatibility complex (MHC). The goal of this research is to develop a high-throughput method to study peptides that are recognized by the body as “self.” Understanding how the immune system distinguishes between “self”—the body’s own
- **Biodefense Proteomics Collaboratory.** This program supports research to dissect immune responses to viruses that are potential agents of bioterrorism, utilizing proteomics approaches to characterize dynamic changes in protein expression in inflammatory cells after pathogen exposure. This information will be compiled in a publicly available database. Bioinformatics approaches also will be used to correlate observed changes in protein expression with available data on changes in gene expression due to inflammation induced by viral infection or endotoxin shock.
- **Proteomics Research Centers.** This program utilizes proteomics technology to identify proteins associated with the biology of microbes, host innate and adaptive immune response, and mechanisms of microbial pathogenesis with the goal of identifying targets for therapeutic interventions. These projects will utilize and augment existing technologies or create novel proteomics approaches to perform early-stage validation studies for identified proteins and cellular targets. To assist the centers, an Administrative Resource for Biodefense Proteomics Research Centers has been established. This resource maintains a publicly available Web site that contains data and technology products generated by the Proteomics Research Centers. It also monitors and facilitates the deposition of reagents and protein targets in a central repository. The Administrative Resource coordinates programmatic meetings and the establishment of a scientific advisory board. For more information, visit: [www.niaid.nih.gov/dmid/genomes/prc/centers.htm](http://www.niaid.nih.gov/dmid/genomes/prc/centers.htm).

organs, tissues, and cells—and “non-self”—foreign and potentially harmful agents—is relevant to all immune-mediated diseases.

- **Bioinformatics Resource Centers for Biodefense and Emerging or Re-emerging Infectious Diseases.** The NIAID Bioinformatics Resource Centers (BRCs) focus on data related to multiple organisms selected from the NIAID lists of Category A, B, and C priority pathogens and other pathogens causing emerging and re-emerging diseases. Each center maintains data related to a selection of pathogens. The BRCs are supported by multidisciplinary teams consisting of pathogen domain experts, microbiologists, bioinformaticians, and computer scientists. For more information, visit [www.niaid.nih.gov/dmid/genomes/brc](http://www.niaid.nih.gov/dmid/genomes/brc).
- **Pathogen Functional Genomics Resource Center (PFGRC).** The PFGRC is a centralized facility providing the research community with resources necessary to conduct functional genomics research on human pathogens and invertebrate vectors of infectious diseases. It provides scientists with genomic resources and reagents such as microarrays, protein expression clones, genotyping, and bioinformatics services. The PFGRC also supports the training of scientists in the latest techniques in functional genomics and emerging genomic technologies. For more information, visit [www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm](http://www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm).
- **Systems approaches to innate immunity, inflammation, and sepsis.** This program supports research to create a comprehensive picture of innate immunity, the body's first line of defense against bacterial, viral, and fungal diseases. This multidisciplinary systems biology approach will lead to an understanding of molecular-level innate immune responses triggered by bacterial and viral infections, as well as the mechanisms by which the innate immune system influences adaptive immune responses. This program has produced more than 70 mutant mouse strains, and over 50 mutations have been mapped to chromosomes. Novel innate immune system molecules and signaling pathways have been identified through analysis of these animal models. For example, a single protein acts as a key switch point in innate immune responses to both bacterial and viral infections. In determining how this protein functions, the team of scientists learned why certain symptoms, such as fever, occur regardless of the cause of infection. This program has also generated recombinant forms of innate immune receptors. These recombinant molecules are used for structural and interaction studies, as well as for the production of monoclonal antibodies. The high-throughput data, protocols, software tools, reagents, and animal models produced by this collaboration are available at [www.innateimmunity-systemsbiology.org](http://www.innateimmunity-systemsbiology.org).
- **Alliance for Cellular Signaling (AfCS).** AfCS is a large-scale collaborative program co-funded by the National Institute of General Medical Sciences (NIGMS), NIAID, the National Cancer Institute, several pharmaceutical companies, and private sources. The primary goal of the AfCS is to dissect signaling pathways in mammalian cells in order to understand how cells interpret and respond to external signals. All of the materials and information developed through the AfCS are freely available to the biomedical community worldwide. More information is available at [www.signaling-gateway.org](http://www.signaling-gateway.org).
- **NIGMS Protein Structure Initiative.** NIAID contributes to the support of this NIGMS-sponsored program to determine the structure of proteins from the genomes of pathogenic protozoans and malaria parasites. The program involves computer prediction of protein domains for target selection, high-throughput protein expression, crystallization,

and structural analysis. More information is available at [www.nigms.nih.gov/psi](http://www.nigms.nih.gov/psi).

- **Bioinformatics Integration Support Contract (BISC).** The goals of the BISC are to advance the discovery and testing of new therapies for immune-mediated diseases and to further understanding of the basis of innate and adaptive immunity by providing advanced computer support for scientific data handling and disseminating best practices in scientific data analysis. BISC will provide the means for scientists to easily access, generate, analyze, and exchange complex high-quality datasets. Specifically, BISC will provide a data repository, a suite of bioinformatics analysis and data integration tools, consulting advice on technical and data management issues, and an archive facility to scientific researchers funded by the NIAID Division of Allergy, Immunology, and Transplantation and the National Institute of Diabetes and Digestive and Kidney Diseases. For more information, see [www3.niaid.nih.gov/about/organization/dait/bisc.htm](http://www3.niaid.nih.gov/about/organization/dait/bisc.htm).
- **HIV Database and Analysis Unit.** This unit includes the HIV Genetic Sequence Database and the HIV Molecular Immunology Database. The Genetic Sequence Database compiles sequence information from GenBank and other international databases and then conducts indepth analyses of HIV genomes. The Molecular Immunology Database compiles all published immunologic information on humoral and cellular immune epitopes from HIV proteins. These databases also provide analysis tools to the user community at [hiv-web.lanl.gov](http://hiv-web.lanl.gov) and [hiv-web.lanl.gov/immunology/index.html](http://hiv-web.lanl.gov/immunology/index.html).
- **Modular gene assembly.** Researchers are developing a new system for engineering genes on the basis of their binding and activation properties. This technology will enable the formation, selection, and assembly of genes based on individual functional traits, which could lead to the development of novel therapeutic compounds such as custom antibodies and immunosuppressants.
- **Microchip drug delivery system.** This program supports development of a novel drug delivery device that uses silicon-based microchips to deliver complex regimens of bioactive agents to specific organs or tissues. Researchers have demonstrated that a silicon-based microchip device with no moving parts can be operated *in vivo*. This device will allow for controlled delivery of a concentrated amount of drugs or bioactive compounds to affected tissues, and has the advantage of eliminating possible toxic side effects and inefficient delivery of systemically administered compounds.
- **Immune Epitope Database and Analysis Program (IEDB).** The primary goals of this program are to develop and maintain an integrated, Web-based, searchable database of antibody binding sites (antibody epitopes) and antigenic MHC-binding peptides (T cell epitopes) for a wide variety of infectious agents and immune-mediated diseases, with emphasis on NIAID category A, B and C priority pathogens, as well as emerging and re-emerging infectious diseases (excluding HIV epitopes, which are catalogued through the HIV database and analysis unit). It is anticipated that the information contained within the database and the availability of analysis tools will facilitate the identification of novel vaccine candidates and immunotherapeutic strategies to improve biodefense strategies. The IEDB website is: [www.immuneepitope.org](http://www.immuneepitope.org).
- **Innovations in Biomedical Computational Science and Technology.** This 2003 trans-NIH program announcement was developed in response to a report by the NIH Working

Group on Biomedical Computing. The report noted the continued need to improve the interface between biomedical research and biomedical information science and technology. This program promotes research and development in database design,

graphical interfaces, query approaches, data retrieval, visualization, integration, and manipulation. One DAIT-funded project performs computational modeling of the physical and chemical interaction of viral proteins with cells of the immune system.

## DRUG RESEARCH AND DEVELOPMENT

The discovery of sulfanilamide, penicillin, and other antibiotic drugs in the early 20<sup>th</sup> century revolutionized the treatment of infectious diseases and gave doctors powerful new tools that for the first time allowed them to easily defeat bacterial infections that would otherwise have been life-threatening. More recently, drugs have been developed that can combat viruses such as influenza and HIV, as well as fungal and parasitic infections. Unfortunately, many infectious agents have become resistant to current therapies, thereby threatening to destroy the effectiveness of these original “wonder drugs.” Also, the immune system can itself cause illnesses such as diabetes, arthritis, and multiple sclerosis when it inappropriately attacks the body’s own tissues.

The development of new therapies for the treatment of infectious and immune-mediated diseases is therefore one of NIAID’s highest priorities. Basic research is the foundation for drug development. Through scientific advances in microbiology, virology, and immunology, scientists identify potential targets for therapeutic agents and new strategies for treating infectious and immune-mediated diseases. Often in collaboration with industry, academia, and other government agencies, NIAID carries out many research programs that facilitate drug development and help maintain related resources, including databases of chemical structures that can be screened for use as therapeutic agents, facilities to conduct preclinical testing of promising drugs, and clinical trial networks to evaluate the safety and efficacy of drugs and therapeutic strategies. Because drug development is a key component of NIAID’s mission, each NIAID Division is actively involved in the drug development process.

## Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes a substantial portion of its resources to the discovery and development of new therapies and/or treatment strategies for people with HIV/AIDS, including treatments for AIDS-associated opportunistic infections (OIs) and co-infections, as well as complications of antiretroviral therapy. The goal of DAIDS’ therapeutic research effort is to foster the discovery and development of treatments to improve the quality and duration of life of HIV-infected individuals. To fuel the drug discovery and development pipeline, NIAID awards investigator-initiated research grants as well as grants and contracts in targeted areas addressed through various program solicitations.

A strong portfolio of basic research is the foundation for DAIDS drug development activities. Over the past 16 years, drug discovery efforts have concentrated on a relatively small number of HIV targets, especially reverse transcriptase (RT), the enzyme that makes a DNA copy of the viral RNA genome after it invades a cell, and protease (PR), the enzyme that activates immature HIV precursor proteins.

A combination of RT and PR inhibitors known as highly active antiretroviral therapy, or HAART, has revolutionized the treatment of people with HIV, successfully suppressing the virus and decreasing the incidence of opportunistic infections in many people in developed countries. These drugs, however, do not constitute a magic bullet. Many patients suffer metabolic abnormalities and toxicities, and some have difficulty adhering to the complex drug regimens required. Strains of HIV that are resistant to therapy can also emerge.

Fortunately, new classes of therapeutic agents have recently entered the development pipeline. Some of these interfere with virus binding and entry into the cell, while others act on viral

targets such as HIV integrase, an enzyme that incorporates the HIV genome into a host cell's DNA. Stopping HIV before it integrates into a host cell is an attractive strategy because it would potentially protect healthy cells from infection and thereby prevent immune system dysfunction. Therapeutic vaccines, which attempt to spur the immune system of an infected person to mount a more vigorous defense, are a potential immunologic approach to complement drug treatment. Even as these advances continue, so too, does the need for discovering new host and viral targets, novel drugs and delivery systems, and immunologic approaches to address the dual problems of drug resistance and toxicity.

The pathways that lead to new HIV drug therapies are many and varied, but all begin with basic research. The research includes studies of the structure and function of viral and cellular proteins critical to the HIV life cycle, immunopathogenic studies to understand how the virus disables the immune system, genetic studies—both human and viral—to define which genes affect susceptibility to infection and disease progression, and studies to understand how to restore effective immune function.

DAIDS pursues these approaches to targeted drug discovery through investigator-initiated grants, Small Business Innovation Research grants, and contracts. Currently, DAIDS is supporting the Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP). The IPCP supports the preclinical evaluation, development, and pilot-stage clinical study of novel agents and strategies to suppress HIV replication, interfere with disease progression, reconstitute or repair immune system damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is identified and moves into preclinical development, it is systematically varied in small ways in an effort to improve its overall activity, safety, and effectiveness. These variations on a theme are subjected to additional *in vitro* testing, evaluating

the agent's activity against a range of HIV isolates in different cell lines and animal models. If appropriate, the IPCP supports early clinical evaluation in human studies.

DAIDS provides contract resources for *in vitro* and *in vivo* screening and testing and evaluation of potential therapeutic compounds. DAIDS has an in-depth array of resources available to investigators to evaluate novel synthetic compounds and purified natural products as anti-HIV, anti-OI, and anti-tuberculosis (TB) therapies, as well as topical microbicides. Also offered are resources to assess therapies for their effects on immunologic functions. DAIDS offers assistance with animal model evaluation of novel antiviral, anti-infective, anti-tubercular, immune-based therapies and topical microbicides in a number of animal models, including rodents, dogs, and nonhuman primates. Potential therapies can also be evaluated for effects on immunologic parameters as a component of animal efficacy studies. Extensive toxicology and pharmacology testing can be conducted to aid in the evaluation of promising anti-HIV agents, anti-infectives, immune-based therapies, and topical microbicides. DAIDS' focus is on assisting investigators in fulfilling the current testing requirements necessary for Investigational New Drug (IND) application filing. An array of chemistry, formulation, and manufacturing resources are available to assist investigators. Each of these services can be performed under Good Laboratory Practice and Good Manufacturing Practice conditions. DAIDS can also facilitate access to clinical virology, immunology, and pharmacology research laboratory evaluations; provide laboratory assay protocols; and aid in developing new diagnostic and therapeutic monitoring methods. Contract resources are also devoted to supporting clinical research on therapeutic interventions for *Mycobacterium tuberculosis* (*M.tb*) infection and co-infection with HIV (see [www.taacf.org](http://www.taacf.org)). This support includes high-throughput screening of anti-*M.tb* compounds and testing in animal models. For

additional information on *M.tb* research, see the “Tuberculosis” section on page 133.

DAIDS also supports therapeutics discovery and development by helping to acquire, share, and disseminate resources for promising treatments for treating HIV infection and associated opportunistic pathogens. To assist investigators during initial research design, DAIDS created and maintains computerized databases of compounds screened for anti-HIV, anti-infective, and anti-TB activity. The databases were established to monitor developments in the chemotherapy of HIV and OIs, to track compounds for further study, and to serve as an information source. They contain chemical structures, *in vitro* efficacy and cellular cytotoxicity test results, as well as *in vitro* and *in vivo* resistance data. The anti-HIV database contains more than 15,000 compounds; the anti-TB database, nearly 50,000 compounds; and the anti-OI database, greater than 10,000 compounds. DAIDS also has access to other chemical and biological databases containing information on more than 500,000 additional compounds. The Division’s scientific research staff is available to assist in accessing nonproprietary information contained in these databases and to help guide drug discovery and development efforts. References in the scientific literature are also available. For more information on the anti-HIV and anti-OI drug databases, visit [http://chemdb2.niaid.nih.gov/struct\\_search/default.html](http://chemdb2.niaid.nih.gov/struct_search/default.html).

Additionally, the NIH AIDS Research and Reference Reagent Program provides state-of-the-art biological and chemical materials for the study of HIV and related opportunistic pathogens. These reagents are available to registered users worldwide at no cost. The AIDS reagent program also serves as an information resource for scientists, a liaison to communicate the needs of investigators in establishing research partnerships, and a provider of technical assistance on handling and shipping infectious

substances. Additional information is available at [www.aidsreagent.org](http://www.aidsreagent.org).

The evaluation of new drugs and therapeutic agents in people is a critical aspect of the DAIDS therapeutics research agenda. These clinical studies define which new agents are effective against HIV and its associated complications and also clarify how best to use these drugs. During the past decade, DAIDS-sponsored therapeutics research has already had a dramatic impact on understanding the pathogenesis and clinical management of HIV infection. Clinical trials research networks funded by DAIDS have defined guidelines for (1) the treatment of primary HIV infection and associated opportunistic infections, (2) prophylaxis of secondary infections, (3) measurement of biological markers, such as CD4+ counts and viral load for predicting a drug’s effectiveness and disease progression, and (4) the use of antiretroviral drugs for preventing mother-to-infant transmission. DAIDS-supported clinical trials programs can address treatment research questions in a variety of different patient populations. Therapeutic candidates (or combination therapies) that fit the mission and focus of these programs may qualify for testing in phase I, II, and III trials. Currently the DAIDS-sponsored therapeutics clinical trial networks include the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, and the Terry Bein Community Programs for Research on AIDS.

NIAID is now in the process of restructuring all of its clinical trials networks to improve the coordination, efficiency, and flexibility of its research networks. Over the past 2 years, DAIDS has worked diligently with its stakeholders and advisory committees to address these issues, delineate six high-priority areas of clinical science, and develop new organizational and managerial strategies to support NIAID’s HIV/AIDS clinical research agenda. In restructuring the HIV/AIDS clinical trials networks, NIAID

seeks to stimulate new collaborative approaches; leverage the networks' substantial complementary strengths and resources; and coordinate HIV/AIDS prevention, vaccine and therapeutic research across multiple study participant/patient populations (e.g., age, gender, ethnicity, risk factors). Awards for the new Leadership for HIV/AIDS Clinical Trials Networks are planned for 2006, while awards for the new Clinical Trial Units are planned for early 2007.

## Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports the discovery and evaluation of new drugs for infectious diseases at all three phases of the process: discovery (disease pathogenesis, target identification, characterization, and screening), preclinical evaluation (testing of human infections in animal models), and clinical evaluation (evaluation of new therapies). Because DMID's mandate encompasses a broad array of infectious diseases, the Division's drug development efforts address the entire spectrum of infectious diseases, including hepatitis, herpes, TB, sexually transmitted infections, malaria, fungal diseases, viral respiratory infections, hospital-associated bacterial infections, and pneumonia. Moreover, the Division's activities support all stages of drug discovery and development, from the test tube to the bedside and, especially for animal model and clinical research, involve close collaborations with the pharmaceutical industry and the Food and Drug Administration (FDA). Finally, in FY 2005, DMID supported approximately 40 large-scale genome-sequencing projects; the genomic information obtained has great potential for further advancing the discovery and evaluation of new therapeutic agents for infectious diseases.

### Discovery and Preclinical Evaluation

DMID-funded research includes basic research on molecular targets, molecular modeling, drug design and synthesis, and mechanisms of

resistance, as well as the development of advanced spectrometric technologies for obtaining higher resolution structural information. This work is supported primarily through the investigator-initiated research program. DMID supports basic and applied research on the discovery and design of antiviral agents; these projects have led to the design of new drugs for influenza, cytomegalovirus (CMV), poxvirus, and hepatitis. Preclinical evaluations of antiviral therapies also are conducted in animal models of human viral infections. In FY 2005, experiments in a mouse model showed that an antiviral drug currently used against annual influenza strains also can suppress the deadly influenza virus that has spread from birds to humans. Since early 2004, this avian flu virus has killed more than a hundred people in Southeast Asia and the Middle East.

DMID maintains an active antiviral screening program that tests potential antiviral agents *in vitro* for activity against many different viruses, including herpes simplex viruses (HSV-1, HSV-2, varicella-zoster virus, Epstein-Barr virus, CMV, human herpesvirus [HHV]-6, HHV-8); respiratory viruses (influenza A and B, respiratory syncytial virus, parainfluenza virus, measles, rhinovirus, adenovirus, sudden acute respiratory syndrome coronavirus); hepatitis B and C; papillomaviruses, BK virus, orthopoxviruses (vaccinia and cowpox); and other viruses that cause hemorrhagic fevers and encephalitides, including West Nile virus. DMID also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases antiviral program in the search for therapies for exotic viruses such as Ebola and Sin Nombre. DMID and DAIDS staff members also interact closely on drug discovery research and therapeutic evaluation efforts for HIV therapies.

Basic research on pathogen replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites, which in turn opens up new possibilities for the development of drugs that attack these targets. DMID

continues to fund research on the development of new methods and improvement of existing ones for the therapeutic treatment of malarial infections. Projects include identification and characterization of unique parasite pathways that can serve as targets for drugs, determination of the mode of action of existing and potential drugs, and analysis of the mechanisms by which parasites have become resistant to existing drugs.

The emergence of antibiotic-resistant pathogens, including those that cause pneumonia and TB, has become a serious global health threat. Methicillin-resistant *Staphylococcus aureus*, for example, has rapidly emerged as a community-associated infection, and in two separate instances *S. aureus* has acquired genes that make it resistant to the powerful antibiotic vancomycin. Public health officials fear that a strain of *S. aureus*—or some other pathogen—might arise that resists all antibiotics currently available.

In response, the Public Health Service, under the leadership of the NIH, FDA, and the Centers for Disease Control and Prevention (CDC), developed an antimicrobial resistance action plan that provides a blueprint for specific, coordinated government actions to address the emerging threat. The four areas of emphasis are (1) surveillance, (2) prevention and control, (3) research, and (4) product development. NIAID has the lead in the area of research. The original plan, *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues*, as well as the annual progress reports and activity inventory, are available online at [www.cdc.gov/drugresistance/actionplan](http://www.cdc.gov/drugresistance/actionplan). In June 2005, the Interagency Task Force on Antimicrobial Resistance hosted a public meeting to discuss progress in implementing the multi-agency action plan. The task force is cochaired by the NIH (NIAID), CDC, and FDA and includes broad Federal agency representation.

Prompt and accurate diagnosis of an infection is obviously important for good patient care,

because it allows doctors to choose the right antibiotic. But good diagnostic tools also help to preserve the efficacy of current therapies by helping to limit the exposure of pathogens to inappropriate treatments and aiding in the identification of patient populations for the evaluation of new antimicrobial agents. In FY 2005, DMID awarded nine grants through a new research initiative called “Sepsis and CAP: Partnerships for Diagnostics Development,” which supports industry development of broad diagnostic technologies for early detection of major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia.

### **Clinical Studies**

DMID supports clinical research with both individual grants and contract-supported programs such as the Collaborative Antiviral Study Group (CASG). The CASG, supported by a single award to the University of Alabama at Birmingham, is a multi-institute, collaborative network composed of more than 60 institutions under which clinical studies of therapies for viral infections are conducted. For example, the CASG supports clinical trials that assess the safety and efficacy of an experimental immunoglobulin treatment for West Nile virus encephalitis and help to elucidate its natural history. For more information about the CASG, visit [www.niaid.nih.gov/daids/pdatguide/casg.htm](http://www.niaid.nih.gov/daids/pdatguide/casg.htm).

The NIAID Mycoses Study Group (MSG), funded by both DMID and DAIDS, has supported clinical trials of antifungal therapies for opportunistic and endemic mycoses (fungal infections) since the 1970s. In early 2001, in conjunction with the scheduled completion of the MSG contract, two contracts were awarded: the Bacteriology and Mycology Study Group (BAMSG) and the Bacteriology and Mycology Biostatistical and Operations Unit (BAMBU). The BAMSG continues to conduct clinical trials of interventions for serious fungal diseases as well as healthcare-associated resistant bacterial

infections. The BAMBU provides biostatistical and administrative support for these clinical trials.

Also, NIAID is sponsoring a trial to test the effectiveness of two infection control strategies for reducing methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* colonization and infection in intensive care units. The Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units (STAR\*ICU) Trial involves 20 hospitals working in collaboration with the NIH Clinical Center.

Other DMID-supported research groups that conduct drug and vaccine evaluations as part of their overall mission include the Vaccine and Treatment Evaluation Units, the International Centers for Infectious Diseases Research, the Sexually Transmitted Diseases (STD) Cooperative Research Centers, and the STD Clinical Trials Unit. NIAID is conducting a phase III efficacy trial using the STD Clinical Trials Unit to determine whether azithromycin, a drug approved for treatment of other infections, is as effective for early syphilis therapy as the usual penicillin treatment; this trial continues to enroll patients. In FY 2003, NIAID launched a pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes. This trial has expanded from 25 sites to more than 40 sites across the United States and Canada, and is being conducted as a public-private partnership with GlaxoSmithKline, using DMID clinical sites. In addition, single-project grants and contracts support therapeutic evaluations for a number of other diseases.

### **Potential Directions for Future Research**

In FY 2005, DMID requested a study by the National Academy of Sciences (NAS) to explore potential new directions in the study of antimicrobial therapeutics. As a part of this study, the NAS hosted two workshops in 2005: one on the potential targets within immunomodulatory/host-mediated response pathways that could

yield broad-spectrum antimicrobial therapies and another on potential new classes of antimicrobials based on pathogen metabolic pathways. When completed, the findings of this study will provide insight into promising new avenues of research in the field of antimicrobial/anti-infective development.

### **Division of Allergy, Immunology, and Transplantation**

The Division of Allergy, Immunology, and Transplantation (DAIT) supports research and development for drugs and biologics to treat and prevent diseases mediated by the immune system, such as autoimmune diseases; primary immunodeficiencies; asthma and allergic diseases; and rejection of transplanted organs, cells, and tissues. DAIT has established several collaborative research groups to study the molecular and immunologic mechanisms that underlie the effects of immunotherapeutic agents currently being evaluated in clinical trials.

Several investigations to evaluate new and potentially more effective therapies for asthma and allergic diseases are currently underway, including immune-based therapies and the development of new medications that inhibit or stimulate specific immune system biochemical systems. DAIT-supported Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to the prevention and treatment of autoimmune diseases. Researchers in these centers have expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes.

DAIT supports several clinical trials programs that test candidate therapies to limit immune-mediated morbidity and mortality of organ transplantation. These programs evaluate novel immunomodulatory strategies to prevent acute rejection and chronic graft loss. Strategies being

examined include biological inhibitors of immune system activation, drug avoidance or minimization regimens to reduce problems associated with the immune system suppression needed to prevent rejection, and pre-transplant induction therapies to facilitate organ transplantation, prevent acute rejection, and promote immune tolerance. Through the Cooperative Clinical Trials in Pediatric Transplantation program, investigators are evaluating these strategies in children needing kidney transplants. DAIT and DAIDS cosponsor the Solid Organ Transplant in HIV program, which is implementing a multicenter prospective cohort study of kidney and liver transplantation in people with HIV. Before the availability of highly active antiretroviral therapy (HAART), HIV-positive patients often were not considered for transplants on the basis of poor prognosis. HAART has significantly increased the longevity of HIV-positive patients, with a subsequent increase in the number of HIV-positive patients with end-stage kidney or liver disease as potential candidates for transplantation. In FY 2004, DAIT established the Clinical Trials in Organ Transplantation program with cosponsorship from the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute to develop and implement interventional and observational clinical studies, accompanied by mechanistic studies, designed to enhance the understanding of and ultimately reduce the immune-mediated morbidity and mortality of organ transplantation. In FY 2004, DAIT and NIDDK launched the Clinical Islet Transplantation program, an international consortium that will design and implement human islet transplantation studies for improved treatment of type 1 diabetes. This consortium will develop and implement single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes.

DAIT, in collaboration with NIDDK, supports the Nonhuman Primate Transplantation Tolerance Cooperative Study Group. The goal of this program is to evaluate the safety and efficacy of new ways to induce immune tolerance of transplanted tissue, using preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. In FY 2005, the program expanded the scope of transplantation models to include nonhuman primate models of heart and lung transplantation and will also provide an opportunity for critical preclinical research to complement NIAID-supported transplantation clinical trials. The program's previous expansion allowed more tolerance-induction strategies to be rigorously evaluated, improved sharing of valuable resources, and helped to forge new collaborations. To further accelerate the research conducted through this program, DAIT supports breeding colonies of specific pathogen-free rhesus and cynomolgus macaques.

DAIT, with cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International, continued to support the Immune Tolerance Network (ITN). ITN is an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and the prevention of graft rejection. The goal of tolerance-inducing therapies is to re-educate the immune system to eliminate harmful immune responses and graft rejection without reducing protective immunity to infectious agents. An important goal of ITN is to explore the immune mechanisms that cause candidate drugs to succeed or fail. ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia.

## Division of Intramural Research

The Division of Intramural Research (DIR) focuses substantial resources on basic studies of the immune system; disease pathogenesis; and microorganism structure, replication, and transmission. These basic investigations, employing animal models and the newest technologies, are key to the discovery of new drugs to treat infectious and immunologic diseases.

### Basic Research for Target Discovery

Basic research on the biology of an organism can lead to the identification of an enzyme, receptor, or other important molecule it needs for replication; these molecules then become prime targets for inhibitory drugs. For example, in 2005, DIR basic research revealed a new target for drug therapy of prion diseases, such as Creutzfeldt-Jakob disease in people and mad cow disease in cattle. DIR scientists found that a variant form of abnormal prion protein—one lacking an “anchor” into the cell membrane—might be unable to signal cells to start the lethal disease process. This research suggests that the blocking the interaction of disease-associated prion protein with membrane-anchored normal prion protein could be a useful target for drug treatment.<sup>28</sup>

### Animal Models of Disease Pathways

Investigation of avian influenza in humans has shown that excessive inflammation might be responsible in part for the acute respiratory distress syndrome and multi-organ failure observed in many patients. Studies of similar disease processes in animal models allow scientists to decipher what biochemical pathways are involved and how they might be disrupted. To identify novel targets to reduce the lethal inflammatory responses accompanying severe respiratory virus infection, DIR scientists are studying the pneumonia virus of mice (PVM), which causes an inflammatory response similar to that seen in severe human respiratory diseases caused by influenza and respiratory syncytial

virus (RSV); the latter is a virus that can cause severe illness in the very young and very old. By administering a biochemical to block this pathway along with the antiviral agent ribavirin, DIR scientists prevented the inflammatory response to PVM, which reduced illness and death in mice. Specific antiviral therapy in conjunction with blockade of this pathway could ultimately prove to be a useful approach to severe respiratory virus disease in humans.

### New Technologies Speed the Discovery Process

New technologies allow more precise characterization of the activity of current drugs, which may lead to the development of more effective formulations. DIR scientists are continuing to uncover the basic modes of action of current TB medications in order to integrate this information with genomic and combinatorial chemistry methods to speed development of second-generation drugs based on similar modes of action. New DNA microarray-based tools for deciphering the molecular mechanisms of anti-tubercular drugs will greatly facilitate these studies. For additional information, see the “Tuberculosis” section on page 133.

### Translating Laboratory Research to the Clinic

To promote translation of laboratory discoveries into products and practices that improve human health, clinical programs are integrated into several of the DIR laboratories. DIR clinician-scientists are conducting more than 80 clinical research protocols at the NIH Clinical Center. Many of these protocols are testing the efficacy of new drug therapies, for example:

- Adjuvant cytokine therapy to boost the innate immune response in pulmonary *Mycobacterium avium* complex infection;

- Separate trials of subcutaneous recombinant interleukin-2, interleukin-7, and leflunomide in HIV infection;
- Peginterferon Alpha 2a and ribavirin induction therapy for chronic hepatitis C in patients who are co-infected with HIV-1; and
- Omalizumab (Xolair) for reducing eosinophil counts and improving symptoms in patients with eosinophilic gastroenteritis.

## EMERGING AND RE-EMERGING INFECTIOUS DISEASES

By the mid-20th century, some scientists thought that medicine had conquered infectious diseases. With the advent of antibiotics and modern vaccines, as well as improved sanitation and hygiene, many diseases that formerly posed an urgent threat to public health were brought under control or largely eliminated. However, the emergence of new infectious diseases and the re-emergence of infectious diseases that previously affected human population have continued, as they have throughout history. Factors such as rapidly changing human demographics; extensive and rapid global travel; changes in land use patterns; mutations in and evolution of the pathogens; resistance to previously effective antibiotics (see page 52); and ecological, environmental, and technological changes are contributing to the emergence of new diseases. These factors, which act as selective pressures, are shaping the evolution of microbes and bringing people into closer and more frequent contact with microbes. Unsanitary conditions in animal agriculture and increasing commerce in exotic animals (for food and as pets) have also increased opportunities for animal microbes to jump from animals to humans. From time to time, with the right combination of selective pressures, a formerly innocuous human or animal microbe can evolve into a pathogen that can cause a major outbreak of human disease.

At times, changes in behavioral and environmental factors can also lead to the re-emergence of diseases that were previously under control. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistant pathogens, allowing many diseases that were formerly treatable with drugs to make a comeback (e.g., tuberculosis, malaria, hospital-acquired and food-borne infections). Recently, decreased compliance with vaccination policy also has led to the re-

emergence of diseases such as measles and pertussis, which were previously under control. Moreover, many important infectious diseases have never been adequately controlled on either the national or international level, leaving open the possibility that those diseases could spread to new locations or re-emerge where they had previously been controlled. There is also potential for the emergence or re-emergence of infectious disease should a deadly pathogen such as smallpox or anthrax be used as an agent of bioterrorism.

To an unprecedented extent, issues related to global health and infectious diseases are on the agendas of world leaders, public health agencies, and nonprofit organizations. This attention has been focused on scientific challenges, such as vaccine development, and on the deleterious effects that infectious diseases can have on economic development and political stability.

### NIAID Programs and Resources for Emerging Infectious Disease Research

NIAID has several programs and resources available to the scientific community to enhance research on a broad array of emerging infectious diseases. These include the following:

- NIAID's national network of 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs) support research focused on countering threats from bioterror agents and emerging infectious diseases. Each RCE is comprised of a consortium of universities and complementary research institutions serving a specific geographical region. The RCEs, located throughout the United States, will build and maintain a strong scientific infrastructure supporting multifaceted research and development activities that promote scientific discovery and translational research capacity required to create the next

generation of therapeutics, vaccines, and diagnostics for biodefense and emerging infectious diseases.

- NIAID's national network of 2 National Biocontainment Laboratories (NBLs) and 13 Regional Biocontainment Laboratories (RBLs). The NBLs will serve as national and regional resources for research on biodefense and emerging infectious disease agents that require biosafety level (BSL)-4/3/2 biocontainment, and the RBLs will serve as a regional resource for research that requires BSL-3/2 biocontainment. These laboratory facilities are being designed and built using the strictest Federal standards, incorporating multiple layers of safety and security to protect laboratory workers and the surrounding environment while conducting research on emerging infectious diseases and Category A, B, and C priority pathogens.
- NIAID's Biodefense and Emerging Infections Research Resources Program supports the acquisition, authentication, storage, and distribution to the scientific community of state-of-the-art research and reference reagents related to biodefense and emerging infectious diseases. Included are the capabilities to validate, expand, and produce biological agents, including cell lines, clones, proteins, monoclonal and polyclonal antibodies, and diagnostic tools.
- Contracts funded under the *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program provide a range of resources for preclinical testing of new therapies, as well as vaccines for biodefense and emerging infectious diseases. Included in this activity are safety, toxicology, and pharmaceutical testing in small and large animals, including the capability for conducting challenge studies.

- NIAID's Food and Waterborne Diseases Integrated Research Network expands the Institute's capacity to conduct clinical research studies of food- and waterborne enteric pathogens.
- NIAID's International Collaborations in Infectious Disease Research (ICIDR) program is a multidisciplinary project to study diseases of major importance to people living in tropical countries. Areas of research supported by the ICIDR program include epidemiology, vector biology, pathology, immunology, diagnosis, and treatment of tropical diseases caused by parasitic, viral, and bacterial infections, including emerging infectious diseases.

## Emerging and Re-emerging Infectious Diseases

### **Severe Acute Respiratory Syndrome—SARS**

In the spring of 2003, the world became aware of an outbreak of a newly recognized pneumonia that was named "severe acute respiratory syndrome," or SARS. The outbreak is thought to have begun in southeastern China's Guangdong province in November 2002, with subsequent spread to the special administrative region of Hong Kong by February 2003, and other countries including Vietnam, Singapore, Taiwan, Canada, and the United States. Epidemiologic investigation showed that the disease disproportionately affected healthcare workers and other close contacts of patients such as family members.

Through an NIAID-supported contract with Dr. Robert Webster at St. Jude Children's Research Hospital in Memphis, researchers at Hong Kong University and their colleagues at four local hospitals were the first to report to the World Health Organization the isolation of a virus that was linked conclusively to SARS patients. Using a high-powered microscope, researchers examined

## List of NIAID Emerging and Re-emerging Diseases 2005

### Group I—Pathogens Newly Recognized in the Past Two Decades

Acanthamebiasis  
 Australian bat Lyssavirus  
 Babesia, atypical  
*Bartonella henselae*  
 Coronaviruses/Severe Acute Respiratory Syndrome (SARS)  
 Ehrlichiosis  
*Encephalitozoon cuniculi*  
*Encephalitozoon hellem*  
*Enterocytozoon bieneusi*  
*Helicobacter pylori*  
 Hendra or equine morbilli virus  
 Hepatitis C  
 Hepatitis E  
 Human herpesvirus 8  
 Human herpesvirus 6  
 Influenza  
 Lyme borreliosis  
 Microsporidia  
 Parvovirus B19

### Group II—Re-emerging Pathogens

*Coccidioides immitis*  
 Enterovirus 71

Prion diseases  
*Streptococcus*, group A  
*Staphylococcus aureus*

### Group III—Agents with Bioterrorism Potential

#### ■ CDC—Category A

*Bacillus anthracis* (anthrax)  
*Clostridium botulinum*  
*Francisella tularensis* (tularemia)  
 Variola major (smallpox) and other poxviruses  
 Viral hemorrhagic fevers  
 Arenaviruses  
 LCM, Junin virus, Machupo virus, Guanarito virus  
 Lassa Fever  
 Bunyaviruses  
 Hantaviruses  
 Rift Valley fever  
 Flaviruses  
 Dengue  
 Filoviruses  
 Ebola  
 Marburg  
*Yersinia pestis*

a culture from a lung biopsy sample and found virus particles whose surfaces were studded with an array of proteins resembling a crown around the virus—a “coronavirus.” The researchers then used antibody tests and other molecular tools to confirm that that this deadly coronavirus (Co-V) was present in at least 35 of the SARS patients they were studying.

Before the emergence of SARS (also called SARS-CoV), human coronaviruses were predominantly associated with up to 30 percent of common colds. Coronaviruses are the largest single-stranded RNA viruses known, and are divided into three serogroups. Recent data indicate that SARS is the prototype strain for a new fourth group of coronaviruses.

In response to the need for rapidly increased research on the SARS coronavirus, in FY 2003, NIAID awarded administrative supplements to

grantees to expand activities on the basic biology and immunology of coronaviruses. NIAID’s grant program supports basic research on animal coronaviruses and the SARS coronavirus. NIAID also supports contracts to develop diagnostics, vaccines, and therapeutics for SARS. In addition, NIAID supports epidemiologic work on SARS and conducts SARS research within its intramural program. Recent accomplishments include:

- **Animal Models.** NIAID Division of Intramural Research (DIR) scientists and their collaborators developed several animal models for SARS, including mouse, hamster, and nonhuman primate models, which allow the evaluation of vaccines, immunotherapies, and antiviral drugs. Using these models, DIR scientists have collaborated with colleagues at NIH, at academic institutions, and in industry to evaluate the immunogenicity

## List of NIAID Emerging and Re-emerging Diseases 2005 (cont'd)

### ■ CDC—Category B

*Brucella* species (brucellosis)  
*Burkholderia pseudomallei* (melioidosis)  
*Burkholderia mallei* (glanders)  
*Coxiella burnetii* (Q fever)  
 Epsilon toxin of *Clostridium perfringens*  
 Food-borne and Waterborne Pathogens  
 Bacteria  
   *Campylobacter jejuni*  
   Diarrheagenic *E. coli*  
   *Listeria monocytogenes*  
   Pathogenic vibrios  
   *Salmonella*  
   *Shigella* species  
   *Yersinia enterocolitica*  
 Protozoa  
   *Cryptosporidium parvum*  
   *Cyclospora cayatanensis*  
   *Entamoeba histolytica*  
   *Giardia lamblia*  
   Microsporidia  
   Toxoplasma  
 Viruses (calciviruses, hepatitis A)  
 Additional viral encephalitides  
   California encephalitis  
   Eastern equine encephalitis

Japanese encephalitis virus  
 Kyasanur Forest virus  
 LaCrosse virus  
 Venezuelan equine encephalitis  
 Western equine encephalitis  
 West Nile virus  
 Ricin toxin (from *Ricinus communis*)  
 Staphylococcal enterotoxin B  
 Typhus fever (*Rickettsia prowazekii*)

### ■ CDC—Category C

Emerging infectious disease threats such as Nipah virus, additional hantaviruses, and the following pathogens:

Influenza  
 Other rickettsias  
 Multidrug-resistant tuberculosis  
 Rabies  
 Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)  
 Tick-borne encephalitis viruses  
 Tick-borne hemorrhagic fever viruses  
   Crimean-Congo hemorrhagic fever virus  
 Yellow fever

Pathogens that naturally emerge with, or are engineered for, increased virulence, increased transmission, and/or the ability to evade the immune response.

and efficacy of inactivated, subunit, vectored, and DNA vaccines against SARS as well as several candidate immunotherapies.<sup>30</sup>

- **Therapeutics.** To date, NIAID screening contracts have evaluated more than 20,000 chemicals for anti-SARS-CoV activity. These NIAID-supported investigators have screened more than 1,400 compounds, including all U.S. Food and Drug Administration (FDA)-approved antiviral drugs. Four compounds, thus far, have shown activity and will be studied further. In addition, NIAID is supporting the development of therapeutic strategies such as antisense oligonucleotides that inhibit viral RNA and humanized monoclonal antibodies.
- **Vaccines.** NIAID is partnering with academia and industry to develop vaccines for SARS, using a variety of different vaccine approaches, including SARS vaccines with adjuvants, virus-like particle vaccines, and recombinant protein and bacterial-vector based vaccines.
- **Diagnostics.** NIAID is supporting research on a variety of different diagnostics approaches for SARS, including polymerase chain reaction- and microarray-based tests, antigen identification for serodiagnosis, and identification of genomic and proteomics targets.
- **Surveillance and Epidemiology.** NIAID has expanded its Pandemic Preparedness in Asia contract with St. Jude Children's Research Hospital (Dr. Robert Webster, Principal Investigator) to expand efforts to identify the animal reservoirs for coronaviruses in Asia, establish cell-based laboratory assays to assess the immune response in infected patients, and

conduct seroepidemiologic studies of family members and other close contacts of SARS patients to assess the rates of asymptomatic infections.

For more information on SARS research updates and opportunities, visit [www.niaid.nih.gov/dmid/sarsapps.htm](http://www.niaid.nih.gov/dmid/sarsapps.htm) and [www.niaid.nih.gov/factsheets/sars.htm](http://www.niaid.nih.gov/factsheets/sars.htm).

### **West Nile Virus**

In the early summer of 1999, a mysterious cluster of cases of encephalitis (inflammation of the brain) and related deaths appeared in New York City, raising the concern of public health officials. Within a short time, researchers identified the cause of the outbreak as West Nile virus (WNV), a flavivirus family virus common in Africa, West Asia, and the Middle East, but never before observed in North America. Symptoms of WNV infection are usually mild, including fever, headache, body aches, skin rash, and swollen lymph glands. If WNV enters the brain, however, it can cause life-threatening encephalitis or meningitis (inflammation of the lining of the brain and spinal cord). These more severe complications of the disease most often affect elderly or immunocompromised individuals.

WNV is transmitted to humans by mosquitoes, which pick up the virus from infected birds. Although the route by which WNV entered the United States is not known, it is thought that the virus may have been introduced by an infected bird that was imported into the country, by an infected mosquito that stowed away on a shipment or transport vehicle entering the country, or by an infected human returning from a country where the virus is common. Since WNV first appeared in the United States, there have been annual outbreaks of the disease, and it has spread across the United States. Experts believe WNV has now become established in North America as a seasonal epidemic that flares up in the summer and continues into the fall.

Because WNV is now well-established in the United States, scientists and health experts at NIAID, along with public health officials, have continued to enhance research on WNV and other arthropod-borne viruses. There are currently no drugs to treat the virus and no vaccines available to prevent infection in humans. However, NIAID supports a robust WNV research portfolio that is aimed toward increased understanding of WNV and developing vaccines, diagnostics, and therapeutics for WNV. The following points summarize key research in several different areas:

- **Basic research.** NIAID conducts basic research on WNV, which leads to a better understanding of the host, pathogen, and environmental factors that influence disease emergence. Basic research determines which flavivirus proteins contribute to the virus's ability to cause disease, and examines how protective immune responses are elicited within the central nervous system during acute flavivirus encephalitis.
- **Animal models.** A golden hamster model has been developed by NIAID-supported researchers and is used for screening drugs and for examining factors that contribute to immunity. This model has proven useful in evaluating strategies for preventing the complications associated with this emerging infectious disease.
- **Vaccines.** NIAID provided initial support via a 3-year, fast-track grant (2000–2003) to Acambis, Inc. to develop a live, attenuated recombinant vaccine for WNV. The resulting chimeric vaccine (a vaccine composed of parts from two or more different organisms) is derived from the well-established Yellow Fever 17D vaccine, in which the envelope genes of the Yellow Fever vaccine virus were replaced with those of the West Nile virus. The WNV vaccine candidate demonstrated good safety, efficacy, and protection against

disease in animal models. The company that developed the vaccine is conducting a phase I clinical trial of the vaccine in humans (started in November 2003), with excellent results so far with regard to safety and immunogenicity. In addition, the NIAID Vaccine Research Center is partnering with industry to develop a DNA vaccine for WNV. A clinical trial of this vaccine began in April 2005.

- **Therapeutics.** NIAID is supporting *in vitro* screening of chemical compounds for possible antiviral activity against several viruses, including WNV, through the NIAID Collaborative Antiviral Testing Group contracts. More than 2,000 compounds had been screened (as of July 2005). A small number (approximately 1 to 2 percent) demonstrated some antiviral activity *in vitro* and are undergoing further testing *in vivo* in mice and hamster models of disease. One of the compounds appears to be particularly effective in the hamster model of WNV disease. NIAID also is supporting research on immunotherapeutics.
- **Center Programs.** NIAID supports the World Reference Center for Emerging Viruses and Arboviruses, which provides basic/applied research capability on arboviruses (including WNV) and other emerging viruses; provides technical support/expertise for investigations of virus outbreaks throughout the world; enables the collection, generation, maintenance, and distribution of a repository of viral and other reference materials; provides a forum to train investigators in virus identification and characterization techniques; and provides clinical trial support.
- **Research Centers.** NIAID also supports two Emerging Viral Diseases Research Centers, which provide broad-based, interactive, multidisciplinary research teams with the scientific expertise needed to study the

emergence of a wide variety of zoonotic and arthropod-borne viral pathogens and other emerging viral threats. Both center contracts also provide the capacity to redirect funds and resources in the event of an urgent public health threat from either natural disease or bioterrorist release. These contracts cover several important areas of research, including basic biology of the virus, WNV ecology and pathogenic/epidemic potential, diagnosis, prevention, and therapy.

- **Insect vectors.** NIAID supports research aimed at better understanding the insect vectors of WNV transmission in affected areas. Such an understanding will allow improved monitoring and surveillance for the vectors and the viruses they transmit.

For more information on West Nile virus and NIAID's research portfolio in this area, see [www.niaid.nih.gov/publications/wnile/default.htm](http://www.niaid.nih.gov/publications/wnile/default.htm) and [www.niaid.nih.gov/factsheets/westnile.htm](http://www.niaid.nih.gov/factsheets/westnile.htm).

### Lyme Disease

Lyme disease is an infection caused by the corkscrew-shaped bacteria *Borrelia burgdorferi*, which are transmitted by the bite of deer ticks (*Ixodes scapularis*) and Western black-legged ticks (*Ixodes pacificus*).

Typically, the first symptom of Lyme disease is a red rash known as erythema migrans. The telltale rash starts as a small red spot at the site of the tick bite and expands over time, forming a circular or oval-shaped rash. As infection spreads, rashes can appear at different sites on the body. Erythema migrans is often accompanied by symptoms such as fever, headache, stiff neck, body aches, and fatigue. After several months of *B. burgdorferi* infection, slightly more than half of people not treated with antibiotics develop recurrent attacks of painful and swollen joints, most commonly in the knees. About 10 to 20 percent of untreated people develop chronic arthritis. Lyme disease can also affect the nervous

system, causing such symptoms as stiff neck, Bell's palsy, and numbness in the limbs. Less commonly, untreated people can develop heart problems, hepatitis, and severe fatigue.

In 2004, the U.S. Centers for Disease Control and Prevention (CDC) reported 19,804 cases of Lyme disease throughout the United States. Five states—New York, Pennsylvania, Massachusetts, Connecticut, and New Jersey—accounted for nearly 75 percent of all reported cases.<sup>31</sup>

The major goals of the NIAID Lyme disease research program are to develop better means of diagnosing, treating, and preventing this disease. To accomplish these objectives, the NIAID Lyme disease research portfolio includes a broad range of activities that are essential to increasing understandings of the disease. The studies include both intramural and extramural research on animal models of disease, microbial physiology, molecular and cellular mechanisms of pathogenesis, mechanisms of protective immunity, vectors and disease transmission, efficacy of different modes of antibiotic therapy, and development of more sensitive and reliable diagnostic tests for both early (acute) and late (chronic) Lyme disease.

**Intramural Research Highlights.** NIAID intramural investigators are studying Lyme disease on the NIH campus in Bethesda, Maryland, and at the Rocky Mountain Laboratories (RML) in Hamilton, Montana, where NIAID scientists discovered the etiologic agent *B. burgdorferi* in the early 1980s. RML scientists are using microarray technology to identify genes associated with unique aspects of the pathogenicity of Lyme disease and other relapsing fever microorganisms.

On the NIH campus, NIAID clinical investigators seek to better understand the natural history of Lyme disease and possible causes for persisting symptoms. To this end, three clinical studies currently are ongoing at the

NIH Clinical Center: one to evaluate and treat patients with classic Lyme disease; another to conduct a comprehensive clinical, microbiologic, and immunologic assessment of patients who have suspected chronic Lyme disease despite previous antibiotic therapy; and a third to use gene microarrays to examine the host response in skin biopsies from patients with erythema migrans, the circular skin rash associated with Lyme disease.

Lyme borreliosis and ehrlichiosis will continue to be areas of high priority for basic research for NIAID, especially with regard to (1) the characterization and treatment of acute and chronic infection; (2) the influence of co-infection with other vector-borne pathogens on the diagnosis, treatment, and severity of Lyme disease; and (3) the development of rapid, sensitive, and specific diagnostic tests and preventive strategies (e.g., vaccines and vector control measures).

### **Influenza**

The “flu” is an infection of the respiratory system caused by an influenza virus. Seasonal influenza outbreaks are a leading cause of infectious disease mortality in the United States, causing approximately 36,000 deaths each year. An annual influenza vaccine is the primary means of limiting the impact of the seasonal influenza.



*Child receiving a nasal vaccine for influenza.*

In the past, new, highly virulent strains of influenza to which the human population had little or no prior immunity occasionally have emerged and have led to global outbreaks, or influenza “pandemics.” The most famous of these was the influenza pandemic of 1918–1919 (often referred to as Spanish influenza). The global death toll for this pandemic was between 20–25 million with perhaps billions of people infected. Other influenza pandemics occurred in 1957 and 1968 and were known as the Asian flu and Hong Kong flu, respectively. Although it has been many years since the last influenza pandemic, scientists and public health officials have been aware of the potential for future outbreaks of deadly strains of influenza and have increased their vigilance and preparedness in light of the current influenza outbreak occurring in Asia.

In 1997, a strain of influenza virus that usually only infects birds, called H5N1 avian influenza or “bird flu,” sickened and killed both poultry and humans in Hong Kong. The virus disappeared from Hong Kong after the mass culling of more than 1 million domestic birds, but reappeared in poultry and humans in Vietnam in 2003. As of mid-July 2006, the H5N1 influenza strain had spread to more than 50 countries, where it infected over 200 people and had killed more than half of them. Public health officials are concerned that this avian virus could mutate and develop the ability to spread from person to person, which could result in a fast-moving global pandemic.

NIAID, which supports a robust portfolio of research on influenza, has been very active in research to enhance understandings of avian influenza viruses and develop vaccines against strains of influenza that could be potential pandemic threats. NIAID currently supports influenza research in the following major areas:

- **Basic biology.** NIAID supports basic research on virus structure and function,

viral pathogenesis, and the host response to infection.

- **Surveillance/epidemiology.** NIAID supports research to better understand the natural history and emergence of influenza viruses with pandemic potential and to evaluate community-based strategies for interrupting the spread of influenza. One example of this crucial work to understand and monitor avian influenza viruses is NIAID’s Influenza Pandemic Preparedness in Asia contract, which supports surveillance and research on the avian virus as it unfolds in Asia, tracing its epidemiology, gathering viral samples, and conducting molecular and genetic research to characterize the virus and assist in the development of vaccines and therapeutics.
- **Drug discovery and evaluation.** NIAID supports the development of novel drugs against influenza and the evaluation of these new agents in both *in vitro* screening assays and animal models. To date, NIAID has screened more than 2,000 compounds for activity against influenza. NIAID also supports development of antiviral drugs against influenza.
- **Enhanced vaccine production strategies.** NIAID supports research on technologies that will enable more rapid production of influenza vaccines, including reverse genetics-based seed strain production, mammalian cell culture of seed virus strains, and a baculovirus expression system for production of vaccine components.
- **Vaccine development and evaluation.** Developing new influenza vaccines and strategies has been a major focus of the NIAID influenza program. These strategies include supporting the development of live-attenuated and recombinant vaccines, immunomodulators and adjuvants, cell

culture-based vaccines, and basic research aimed at optimizing the immune response. NIAID is also exploring common epitope or “universal” flu vaccines, a strategy that could result in flu vaccines that provide broad immunity against many strains of influenza viruses. NIAID also supports the production and clinical testing of vaccines against avian influenza subtypes of high pandemic potential. For example, NIAID’s Vaccine and Treatment Evaluation Units have recently completed a clinical trial of a candidate H5N1 avian influenza vaccine in healthy adults. Preliminary data indicate that the vaccine is generally safe and stimulates an immune response. Future plans include testing this H5N1 vaccine in the elderly and in children, populations often most vulnerable to influenza.

In addition, NIAID’s Division of Intramural Research is capitalizing on its decades of research and development of live-attenuated vaccines to develop avian influenza vaccines under a cooperative research and development agreement (CRADA) with MedImmune, Inc. Under the CRADA, DIR and MedImmune scientists will produce and test multiple live-attenuated intranasal vaccines against potential pandemic flu strains, starting with the H5N1 strain (see page 147).

Also, DIR scientists are continuing work begun several years ago following the emergence of an H9N2 avian flu strain in Hong Kong and China that caused several human infections. A live-virus vaccine developed by DIR and CDC scientists against this H9N2 avian virus has completed phase 1 clinical testing for safety and efficacy.

- **Novel vaccine delivery systems.** NIAID-supported researchers are also helping to develop novel techniques to deliver influenza vaccines. For example, beginning in the mid-1970s, NIAID investigators were integral to the development and clinical evaluation of a

live influenza vaccine that can be delivered as a nasal spray. FluMist™ was licensed by the FDA in the summer of 2003, and was available for the first time during the 2003–2004 flu season. NIAID is currently exploring strategies to extend vaccine supplies using dose-sparing approaches such as immunizing people directly into the skin rather than in muscle, or adding substances called adjuvants to vaccines to increase their potency. These strategies could decrease the amount of vaccine required to elicit the desired level of immune response.

For more information on influenza, including weekly reports on flu activity, go to [www.cdc.gov/flu/weekly/fluactivity.htm](http://www.cdc.gov/flu/weekly/fluactivity.htm).

### Prion Diseases

Fatal neurodegenerative diseases such as Creutzfeldt-Jakob disease (CJD) and bovine spongiform encephalopathy (also known as BSE or “mad cow” disease) are referred to as “prion diseases” because they are believed to be caused and transmitted by prion proteins, a new type of infectious agent discovered in the 1980s. Prion proteins enter cells and cause normal cellular proteins to adopt abnormal three-dimensional structures, which in turn leads to disease. In addition to CJD, which affects humans, scrapie and chronic wasting disease (CWD) are other prion diseases that affect animals. Since the onset of the BSE epidemic in the United Kingdom in the 1980s, the disease has resulted in the destruction of millions of animals in Europe. Because the BSE epidemic was temporally and geographically associated with the emergence of a variant form of CJD in humans, health officials believe the disease was spread to humans by infected beef. In May 2003, the finding of BSE in a single cow in Canada resulted in a ban on exportation of certain live ruminants and ruminant products from Canada to the United States. Since then, several other BSE-infected cows have been identified in the United States,

but there has been no evidence of transmission to humans in the United States.

Transmissible spongiform encephalopathy (TSE) research in DIR is conducted at the RML, where scientists are answering fundamental questions about the nature of infectious prions that are key to developing methods to prevent and treat prion-associated diseases. For example, RML investigators are working to determine how abnormal prions are formed and how they cause disease, the mechanisms of and barriers to cross-species transmission, and routes of TSE transmission. RML scientists made several important advances in 2005, including:

- Identification of the smallest and most efficient particles capable of initiating TSE diseases;<sup>32</sup>
- Discovery of a molecule that might play a role in clinical manifestations of prion disease;<sup>33</sup>
- Discovery of novel, potent abnormal prion inhibitors (called degenerate phosphorothioate oligonucleotides);<sup>34</sup> and
- Development of the first cultured cell line infected with CWD, and identification of the first inhibitors of CWD replication.

In addition, an important study to determine whether CWD prion protein can be transmitted to nonhuman primates via oral or intracerebral routes is now in its second year. RML scientists also are using a high-throughput screening method they developed in 2004 to find potential

TSE therapeutics, and studies of antibody and vaccine-based therapies for TSEs are ongoing.

NIAID also provides extramural grant support for investigator-initiated studies of CWD and other prion diseases that seek to better understand prion entry, trafficking, pathogenesis, and transmission, which could provide a basis for development of diagnostic and intervention strategies. In addition, NIH has initiated studies in response to the Department of Health and Humans Services' 2001 BSE/TSE Action Plan, including:

- NIAID support of a 7-year, \$8.4 million contract to Colorado State University to operate an emerging disease research center focused on CWD. The research center in Fort Collins investigates the mechanics of CWD infection in deer and elk, especially in the immune system's lymphoid tissues. Such studies underlie the search for improved diagnostics and therapies. In addition, studies of ecological factors in transmission and evaluation of CWD vaccination strategies in deer are ongoing.
- NIH evaluation of potential anti-TSE compounds in animal models. Through expansion of an NIAID contract with Utah State University, candidate compounds are evaluated for efficacy in transgenic animals that have a shortened time to death. This model was established at Utah State in collaboration with NIAID's RML.

## GENOMICS

### Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports a substantial program in genomics research, including sequencing of human pathogens and invertebrate vectors of diseases; applying genomic, functional genomics, and proteomic technologies to the study of microorganisms and infectious diseases; supporting genomic databases; and providing high-quality genomic reagents and technological resources to the scientific community.

#### Genome Sequencing

A genome is an organism's complete set of genes, encoded as a specific sequence of paired DNA bases. Recent advances in molecular biology have given researchers powerful methods that can quickly and accurately determine the complete DNA sequence of the whole genome of virtually any organism, including disease-causing microorganisms and the insect and other invertebrate vectors that can transmit them.

Whole-genome sequencing is an enormously powerful tool for understanding and defeating infectious diseases. For example, scientists can compare and contrast genomes to identify genes that are unique to a particular microbe. They can then target these genes with specific drugs, incorporate the products of these genes into experimental vaccines, and develop more sensitive diagnostic tests. Moreover, sequence information can reveal small genetic variations between different strains of a given pathogen. Researchers can use these subtle differences to determine which genes affect a pathogen's virulence, which genes are involved in the development of antibiotic resistance, and how a virulent or resistant strain spreads within a susceptible population; better understanding of these phenomena will help to improve disease diagnosis and patient care. Finally, understanding

how microbial genes interact with one another and the human host during infection will lead to new strategies for drug therapies and vaccine development.

To capitalize on the tremendous potential of genome sequencing, NIAID has invested heavily in projects to sequence the genomes of medically important microbes. Sequencing technology has advanced to the point where NIAID working alone can fund the determination of a bacterial species; however, NIAID collaborates with other funding agencies to sequence the larger genomes of protozoan and fungal pathogens. To date, NIAID has completed the sequence of 92 genome-sequencing projects for 75 bacteria, 6 fungi, 9 parasitic protozoa, and 2 invertebrate vectors of infectious diseases. The bacterial species include those that cause anthrax, plague, tuberculosis, gonorrhea, chlamydia, cholera, strep throat, scarlet fever, and food-borne diseases. DNA sequencing projects have also been completed for the protozoan parasites *Cryptosporidium parvum*, *Entamoeba histolytica*, *Leishmania*, *Plasmodium falciparum*, *Giardia*, *Toxoplasma gondii*, *Trypanosoma cruzi*, and *Trypanosoma brucei* and the fungi *Aspergillus fumigatus*, *Aspergillus terreus*, *Cryptococcus neoformans*, and *Histoplasma capsulatum*. NIAID's data release policies ensure that both raw genome sequence data and associated assemblies and annotations are available to scientists around the world through deposition in an appropriate publicly searchable database (GenBank).

Study of the genomics of malaria has been particularly successful; for the first time, researchers have in hand the complete genetic sequences of the infectious organism, its natural host, and the insect that transmits it. In 2002, the International Malaria Genome Sequencing Consortium—funded in part by NIAID—published the genome sequence of *Plasmodium falciparum*, the parasite that causes the most severe form of malaria. NIAID also supported the rapid sequencing of the genome of *Anopheles*

*gambiae*, the mosquito that transmits the malaria parasite to humans. Researchers therefore now have the genome sequences of all three organisms involved in malaria—the mosquito vector, the malaria parasite, and the human host. This provides scientists with a unique opportunity to unravel the complex interactions between these three species on a molecular level. Indeed, NIAID-supported scientists already have taken advantage of this valuable genomic information to gain new insights into the molecular mechanisms involved in insecticide resistance, and to identify genes and gene products that are promising targets for new drug therapies.

The national biodefense effort has benefited substantially from genomic research as well, and NIAID has made a significant investment in sequencing microorganisms with the highest priority as potential agents of bioterrorism. For example, NIAID collaborated with the Office of Naval Research and the Department of Energy to sequence the genome of the Ames strain of *Bacillus anthracis*, the bacterium that causes anthrax. Other organisms sequenced include *Brucella suis*, *Burkholderia mallei*, two strains of *Clostridium perfringens*, *Coxiella burnetii*, and *Rickettsia typhi* with Defense Advanced Research Projects Agency funds; and six strains of *Bacillus anthracis*; *Bacillus cereus* strains; *Mycobacterium tuberculosis*; *Rickettsia rickettsii*; *Staphylococcus aureus*; *Yersinia pestis*; food-borne bacterial pathogens including diarrheagenic *E. coli*, *Vibrio cholerae*, *Shigella*, and *Salmonella*; and parasitic protozoa including *Cryptosporidium parvum* (human and bovine), *Giardia lamblia*, *Entamoeba histolytica*, and *Toxoplasma gondii*. In FY 2005, genome sequencing projects for *Burkholderia thailandensis*, five strains of *Burkholderia mallei* and *Burkholderia pseudomallei*, eight strains of *Escherichia coli*, two strains of *Yersinia pestis*, and one invertebrate vector of disease, *Aedes aegypti*, were completed. *Aedes aegypti* is the primary mosquito vector responsible for transmission of both yellow fever and dengue fever, and is the second invertebrate vector of infectious

diseases sequenced by NIAID. Biodefense genome sequencing projects are currently being supported for additional strains of *Bacillus anthracis*, *Bacillus cereus*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Campylobacter*, *Coxiella burnetii*, *Escherichia coli*, *Entamoeba*, dengue viruses, *Francisella tularensis*, influenza, *Listeria*, *Mycobacterium tuberculosis*, *Ricinus communis*, *Shigella*, *Toxoplasma gondii*, *Vibrio cholerae*, *Yersinia pestis*, and the invertebrate vector, *Culex pipens*.

In FY 2005, NIAID continued to support the Influenza Genome Sequencing Project ([www.niaid.nih.gov/dmid/genomes/mcs/influenza.htm](http://www.niaid.nih.gov/dmid/genomes/mcs/influenza.htm)), which is providing the scientific community with complete genome sequence data for thousands of human and animal influenza viruses. The influenza sequence data are being placed rapidly in the public domain through GenBank, an international searchable database, and NIAID's newly funded Bioinformatics Resource Center, with accompanying data analysis tools that enable scientists to study further how influenza viruses evolve, spread, and cause disease and might ultimately lead to improved methods of treatment and prevention. This newly generated sequence information is providing a larger and more representative sample of influenza virus genomes than was previously available to the public. This project has the capacity to sequence more than 200 genomes per month and is a collaborative effort among NIAID, the National Center for Biotechnology Information of the NIH's National Library of Medicine, The Institute for Genomic Research (TIGR), Wadsworth Center at the New York State Department of Health, Air Force Institute of Pathology, St. Jude Children's Research Hospital in Memphis, Centers for Disease Control and Prevention, Ohio State University, University of Maryland, Canterbury Health Laboratories (New Zealand), Los Alamos National Laboratories, and others. As of October 26, 2005, 463 complete genome sequences for influenza viruses had been released to GenBank, which include H1N1, H1N2, and H3N2 viral genomes collected from human clinical isolates.

## Genomic Research

Obtaining the raw sequence of an organism's genome is only the first step in understanding it; annotating and organizing the sequence data are also required. Furthermore, the sequence data allow researchers to study an organism's proteome—the entire set of proteins that are encoded in the genome sequence. NIAID-supported investigators are applying such emerging genomic technologies to study microorganisms and infectious diseases. These studies include both basic research topics, such as the biology of a pathogen and the host's response to infection, and applied research such as development of medical diagnostics, drugs, and vaccines. Genomic technologies help scientists study infectious agents at the whole genome or proteome level. For example:

- Whole genome and proteome expression studies are being used to identify pathogen-specific genes and proteins involved in virulence, pathogenesis, and disease transmission.
- Proteomic technologies are being applied to both the pathogen and the host proteome to allow identification of candidate protein targets for new vaccines, therapeutics, and diagnostics.
- Genomic technologies are providing platforms for examination of genetic variation within and between species, strains, and clinical isolates, as well as for study of host responses to infection, vaccines, and antibiotic drugs.

## Genomic Resources, Reagents, and Technologies

NIAID facilitates distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens and supports the development of bioinformatics and computational tools that allow investigators to store and

manipulate genomic and postgenomic data. In the past few years, NIAID has expanded its genomics activities and established comprehensive centers to provide the scientific community with needed reagents and resources to conduct basic and applied infectious diseases research. These centers include the NIAID Microbial Sequencing Centers, Pathogen Functional Genomics Resource Center (PFGRC), Bioinformatics Resource Centers, and Proteomics Research Centers.

NIAID continues to support the PFGRC at TIGR in Rockville, Maryland. PFGRC was established in 2001 to distribute to the research community a wide range of genomic and related resources and technologies for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases. Considerable progress has been made toward this goal, including the generation and distribution of 25 organism-specific DNA microarrays; the Center now includes microarrays for viruses, bacteria, fungi, and parasites. The available DNA microarrays include *Aspergillus fumigatus*, *Aspergillus nidulans*, *Chlamydia*, coronaviruses (animal and human), human SARS chip, *Helicobacter pylori*, *Mycobacterium smegmatis*, *Neisseria gonorrhoeae*, *Plasmodium falciparum*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Trypanosoma brucei*, and *Trypanosoma cruzi*. In addition, organism-specific microarrays were produced and distributed for organisms considered agents of bioterrorism and include *Bacillus anthracis*, *Clostridium botulinum*, *Francisella tularensis*, *Giardia lamblia*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Rickettsia prowazekii*, *Salmonella typhimurium*, *Vibrio cholerae*, and *Yersinia pestis*. In addition, PFGRC has developed the methods and pipeline for generating organism-specific protein expression clones. Complete clone sets are now available for human SARS coronavirus, *Bacillus anthracis*, *Yersinia pestis*, and *Streptococcus pneumoniae*. In addition, individual custom clone sets are available for more than 20 organisms upon request.

Further information is available at [www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm](http://www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm).

In FY 2003, NIAID awarded a contract to TIGR to support a Microbial Genome Sequencing Center to allow for rapid and cost-efficient production of high-quality microbial genome sequences; in early FY 2004, NIAID awarded a contract to the Massachusetts Institute of Technology to support a similar sequencing center. Genomes to be sequenced include microorganisms considered agents of bioterrorism (NIAID Category A, B, and C agents), microorganisms responsible for emerging and re-emerging infectious diseases, related pathogens, clinical isolates, and invertebrate vectors of infectious diseases. These sequencing centers have the capacity to respond to national needs and government priorities for genome sequencing, filling in sequence gaps and thus providing genome sequencing data for multiple uses, including forensic strain identification and identification of targets for drugs, vaccines, and diagnostics. In FY 2005, NIAID supported approximately 40 large-scale genome sequencing projects for additional strains of viruses, bacteria, fungi, parasites, viruses, and invertebrate vectors and included new projects for hepatitis C, coronaviruses, *Bacillus anthracis*, *Bacillus cereus*, *Bartonella bacilliformis*, *Burkholderia cenocepacia*, *Burkholderia dolosa*, *Campylobacter*, *Coxiella burnetii*, *Escherichia coli*, influenza, *Listeria*, *Pseudomonas aeruginosa*, *Shigella*, *Vibrio parahaemolyticus*, three strains of *Aspergillus*, additional strains of *Entamoeba*, *Plasmodium falciparum*, *Toxoplasma gondii*, additional sequencing of *Plasmodium vivax* and *Trichomonas vaginalis*, and one strain of *Ricinus communis*. Further information can be found at [www.niaid.nih.gov/dmid/genomes/mscs](http://www.niaid.nih.gov/dmid/genomes/mscs).

The Malaria Research and Reference Reagent Resource Center ([www.malaria.mr4.org](http://www.malaria.mr4.org)) continued to provide expanded access to quality-controlled reagents for the international malaria research community in FY 2005.

### **Bioinformatics and Databases**

In FY 2004, NIAID awarded eight contracts to establish Bioinformatics Resource Centers. These centers develop, populate, and maintain comprehensive relational databases to collect, store, display, annotate, query, and analyze genomic, structural, and related data for emerging and re-emerging pathogens, including those important for biodefense. The centers also develop and provide software tools to assist in data analysis. The databases these centers maintain are a valuable genomic resource, providing the scientific community with easy access to large amounts of genomic and related data and bioinformatics tools for data analysis. Further information is available at [www.niaid.nih.gov/dmid/genomes/brc/default.htm](http://www.niaid.nih.gov/dmid/genomes/brc/default.htm).

### **Genomics and Proteomics**

In the past several years, NIAID has awarded contracts for Biodefense Proteomics Research Centers, which develop and improve proteomic technologies and apply these technologies to pathogen and host cell proteomes for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics, and immunotherapeutics against microorganisms considered agents of bioterrorism. Eight centers have been funded to date; they focus on a range of NIAID category A, B, and C pathogens. Further information is available at [www.niaid.nih.gov/dmid/genomes/prc/default.htm](http://www.niaid.nih.gov/dmid/genomes/prc/default.htm).

### **Division of Allergy, Immunology, and Transplantation**

The Division of Allergy, Immunology, and Transplantation (DAIT) also supports genomics research. The human immune system is composed of complex networks of interacting cells, each programmed by precisely scripted genes. Underlying each immune response to a disease is a multistep pathway of interacting molecules influenced by an individual's unique genomic characteristics. The immune system plays a critical role in diseases such as rheumatoid arthritis; hay

fever; contact dermatitis; insulin-dependent or type 1 diabetes; systemic lupus erythematosus; and graft rejection of transplanted solid organs, tissues, and cells. Each of these diseases has an underlying genetic component.

Genomic research supported by DAIT is yielding insights into the functional and structural dimensions of immune system regulation, hypersensitivity, and inflammation in diseases such as asthma; the dysregulation of immune responses that results in autoimmune disease; and basic mechanisms of immune tolerance and graft rejection. This research is important in the following areas:

- **Asthma and allergic diseases.** DAIT-supported research on the genetics of asthma, hypersensitivity, inflammation, and T cell mediation increases understanding of the mechanisms underlying these immune responses, resulting in improved diagnostic, prevention, and treatment strategies. Through genomic research, DAIT-supported investigators discovered that interleukin-4 (IL-4), a cytokine produced by helper T cells and mast cells, stimulates antibody production by B cells in a series of reactions involving several genes. Further studies on IL-4 might provide a marker for measuring asthma risk and severity.
  - **Autoimmune diseases.** DAIT supports research on type 1 diabetes and other autoimmune diseases that involve more than a single gene. Recent developments in genomics such as high-resolution DNA analysis and bioinformatics tools are making it possible to understand the underlying genetic causes of these complex diseases. For example, one approach compares the genes of individuals who have an autoimmune disease with those of healthy individuals to identify genetic and genomic differences that might be the underlying cause of disease. Between 10 and 20 distinct loci on the human genome
- might be responsible for susceptibility to type 1 diabetes. This knowledge will increase the ability to predict, diagnose, and treat this disease.
- **Transplantation.** DAIT-supported research on the genetics of graft rejection and immune tolerance is breaking new ground in the transplantation of solid organs, tissues, and cells for the prevention and treatment of disease. Genomic research funded by DAIT has identified surrogate markers of graft rejection in kidney transplant recipients. This research holds promise for the development of a noninvasive predictor of graft rejection based on gene expression analysis in urinary cells of transplant recipients.
  - **Basic immunology research.** Basic research in immunology furthers understanding of the properties, interactions, and functions of the cells of the immune system and the genetic aspects of immune system regulation and provides information about essential structural immunobiology. Recent breakthroughs in the basic science of immunogenetics inform clinical immunology, which could lead to the development of new immune-based therapies. Examples of basic immunology research supported by DAIT include:
    - Use of large-scale gene- and protein-expression analysis tools to describe pathways of cellular activation;
    - Discovery of anti-inflammatory and immunosuppressive agents using DNA-based screening methods; and
    - Analysis of genomic databases of T cell receptors and immunoglobulin gene sequences to link structural, functional, and clinical information.

### **Multicenter Research Programs**

DAIT supports several multicenter research programs that include significant genomic efforts aimed at understanding the underlying mechanisms of immune-mediated diseases.

**Immune Tolerance Network (ITN).** The ITN is an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases; asthma and allergic diseases; and rejection of transplanted organs, tissues, and cells. The goal of these therapies is to re-educate the immune system to eliminate harmful immune responses while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the-art core laboratory facilities to conduct integrated mechanistic studies and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. These core facilities include microarray analyses of gene expression, bioinformatics approaches to develop analytic tools for clinical and scientific datasets from the ITN-sponsored trials, enzyme-linked immunospot analyses of protein expression, and cellular assays for T cell reactivity. ITN is cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International. More information on the ITN is available at [www.immunetolerance.org](http://www.immunetolerance.org).

### **Autoimmunity Centers of Excellence (ACEs).**

ACEs support collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of promising immunomodulatory therapies. Clinical trials supported by ACEs include: a phase I/II clinical trial of anti-CD20 for treatment for lupus; phase I clinical trial of anti-tumor necrosis factor for treatment of lupus nephritis; preclinical study of DNase treatment, now underway with a follow-up phase Ib trial planned.

### **Multiple Autoimmune Disease Genetics Consortium (MADGC).**

MADGC is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This resource provides well-characterized material on 363 families to promote research aimed at discovering the human immune response genes involved in autoimmunity. More information can be found at [www.madgc.org](http://www.madgc.org).

### **North American Rheumatoid Arthritis Consortium (NARAC).**

NARAC is a collaborative registry and repository of information on families with rheumatoid arthritis. The NARAC database contains information on 902 families, encompassing 1,522 patient visits. Of the 902 families, data for more than half have been validated, including 600 affected sibling pairs. The family registry and the repository samples should facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis and are available to all investigators. This registry is cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation. More information can be found at [www.naracdata.org](http://www.naracdata.org).

### **Primary Immunodeficiency Diseases Registry and Consortium.**

In FY 2003, the Primary Immunodeficiency Diseases Consortium was established with support from NIAID and the National Institute of Child Health and Human Development. The Consortium (1) provides leadership and mentoring; facilitates collaborations; enhances coordination of research efforts; and solicits, reviews, recommends, and makes awards for pilot or small research projects; (2) maintains a primary immunodeficiency diseases registry, which provides data to the research community about the clinical characteristics and prevalence of these diseases; and (3) is developing a repository of specimens from subjects with primary immunodeficiency diseases. Additional information on consortium activities is available at [www.usidnet.org](http://www.usidnet.org).

## GLOBAL HEALTH

The NIAID research mission in infectious and allergic diseases is of global importance. When combined, these conditions are the most common causes of preventable human illness and death around the world. Recent concern about emerging and re-emerging infectious diseases and the anthrax attacks of October 2001 further reinforced the importance of and added new dimensions to NIAID-supported research in improving early diagnosis, prevention, and control of these pathogens.

Formal recognition of the importance of international research dates back to the International Health Research Act (1960), which gave the Secretary of Health, Education, and Welfare—now the Secretary of Health and Human Services—the authority to conduct research activities outside the United States, provided that the activities were beneficial to the health of U.S. citizens. This authority has been delegated to the NIH and to NIAID. The Public Health Service Act of 1988 (Public Law 100–607) created new HIV/AIDS authorities for the NIH. Subsequently, the NIH Revitalization Act (1993) gave NIAID specific authority to conduct research on tropical diseases that disproportionately affect populations in resource-poor and economically restructuring countries.

In May 2001, NIAID announced its Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis. The Global Plan provides short-, medium-, and long-term objectives for treating, preventing, and controlling these diseases by building on the Institute's strong foundation in infectious disease research.

### Intramural Research Training and Collaborative Research

NIAID laboratories located in the Bethesda, Maryland–greater Washington, D.C., Washington metropolitan area, and Hamilton,

Montana, are a significant source of research training for postdoctoral non-U.S. scientists. NIAID is also responsible for the management of the Dale and Betty Bumpers Vaccine Research Center (VRC). The host NIAID laboratory usually provides the stipend for the visiting scientists. The research training experience often results in long-term intramural international collaborations once the scientists return to their home countries. In FY 2005, the largest numbers of NIAID international scientists were from China, India, Japan, France, Canada, Germany, and Italy.

Several years ago, the NIAID Division of Intramural Research (DIR) initiated the International Centers for Excellence in Research (ICER) program to develop sustained research activities in areas of high infectious disease burden through partnerships with scientists in developing countries. Current ICER sites are in India, Mali, and Uganda, and the ICER program builds on longstanding intramural research collaboration with scientists in those countries. Although DIR provides the core research program at each ICER site, the ultimate goal is to expand the research capabilities and programs at these sites through the involvement of the extramural research community. Each ICER focuses on clinical research in infectious disease and has the capability to address a range of research and training activities.

The VRC, in collaboration with the Makerere University–Walter Reed Project and the NIAID Division of AIDS, announced in FY 2005 the expansion of ongoing U.S. phase I clinical trials of a novel HIV-1 DNA vaccine directed at the three most globally important HIV-1 subtypes (clades) to Kenya, Tanzania, and Uganda.

### Domestic Research Awards with an International Component

NIAID funds the vast majority of its international research indirectly through

competitive domestic extramural research awards that have an international component. Special emphasis programs have been developed in tropical medicine, emerging infectious diseases, HIV/AIDS, and tuberculosis to take advantage of research opportunities overseas in countries with a disproportionate burden of these diseases.

The infectious disease clinical research efforts supported by NIAID include international sites. Initiated in 1994, the NIAID Tuberculosis Research Unit is supported by a research contract with Case Western Reserve University and funds an international cross-disciplinary team of investigators in Brazil, the Philippines, South Africa, Uganda, and the United States to conduct high-priority research. This research addresses complex clinical questions about tuberculosis and provides the scientific framework upon which high-quality clinical trials of new vaccines, therapeutics, and diagnostics can be conducted. The Sexually Transmitted Diseases Clinical Trials Unit also supports sites in Madagascar and Uganda. In addition, the NIAID Bacteriology and Mycology Study Group has ongoing clinical trials in Thailand. Clinical site development continues in Ghana and Mali for malaria vaccine trials.

NIAID also supports a number of research programs that focus on tropical infectious diseases. The International Collaboration in Infectious Disease Research (ICIDR) Program, initiated in 1980, makes awards to U.S. institutions to engage in substantial international collaboration with overseas institutions in tropical medicine and emerging infectious diseases. The ICIDR Program was recompeted in FY 2005, and of 13 projects in the United States and 19 foreign countries were funded.

In the context of conducting international research, NIAID supports the development of independent research capacity at NIAID-funded institutions. Numerous training activities have been conducted in Africa, India, South America,

and Southeast Asia. This training includes good clinical practices, international research ethics, institutional review board administration, scientific writing, the design and conduct of clinical trials, and technology transfer.

NIAID AIDS research networks have both domestic and international components. The HIV Vaccine Trials Network (HVTN) is a comprehensive, clinically based global network with a mission to develop and evaluate preventive HIV vaccines. The HVTN includes international sites located in Africa (Botswana, Malawi, and South Africa), Asia (China, India, and Thailand), the Caribbean (Dominican Republic, Haiti, Jamaica, Puerto Rico, and Trinidad and Tobago), and South America (Brazil and Peru).

The HIV Prevention Trials Network (HPTN) is a second worldwide collaborative effort established by NIAID to evaluate the safety and efficacy of non-vaccine prevention interventions. The HPTN consists of domestic and international units. International sites are located in Brazil, China, India, Malawi, Peru, Russia, South Africa, Tanzania, Thailand, Uganda, Zambia, and Zimbabwe.

NIAID's Acute HIV Infection and Early Disease Research Program is collaborating with the University of Alabama at Birmingham and the University Teaching Hospital in Lusaka, Zambia, to study the effects of a short course of antiretroviral therapy on the viral load in newly infected persons when it is initiated early after HIV infection.

The NIAID Centers for AIDS Research (CFARs) support a multidisciplinary environment that promotes basic, clinical, behavioral, and translational research in the prevention, detection, and treatment of HIV infection and AIDS. Current CFAR collaborations are taking place in Belize, Kenya, Mexico, Peru, Thailand, Uganda, and Zambia.

In 2005, NIAID expanded its Pandemic Preparedness in Asia contract at St. Jude Children's Research Hospital in Memphis. (The original award was made in 1998 for the surveillance and characterization of avian influenza viruses with pandemic potential in the live bird markets in Hong Kong.) Activities conducted under this expansion include establishing animal influenza surveillance sites in Asia, including Indonesia, Thailand, Vietnam, and Indonesia, to generate vaccine candidates against influenza strains with pandemic potential and accompanying reagents; supporting an international animal surveillance training course in Hong Kong (March 2004); and studying the newly emerging influenza strains infecting swine in the United States.

### International Awards

NIAID and the NIH accept investigator-initiated research proposals from international scientists and permit them to respond to most program announcements and requests for applications. To be funded, international applications must receive a competitive peer review score and be approved by the National Advisory Allergy and Infectious Diseases Council on the basis of their uniqueness and/or program relevance. International scientists also may be eligible to compete for NIAID research contracts when U.S. institutions cannot carry out the project (e.g., pertussis vaccine trials in Italy and Sweden) or when the domestic applications are not responsive to the solicitation.

Historically, international awards have accounted for about 1 percent of the NIAID budget. As basic research results in new or improved products that require evaluation in populations with heavy burdens of disease, this amount is increasing. Furthermore, long-term NIAID investment in collaborative research has resulted in the development of overseas sites capable of independent research. The establishment of the Tropical Medicine Research Centers (TMRC) program a decade ago was a reflection of this

phenomenon. Currently, TMRCs are currently located in Brazil, Chile, Colombia, and Peru.

In FY 2001, NIAID launched the Comprehensive International Program of Research on AIDS (CIPRA). CIPRA provides support directly to institutions in developing countries to plan and implement a comprehensive HIV/AIDS prevention and research program. There are ongoing CIPRA awards in 12 different countries. These include five planning and organizational grants in Egypt, Kenya, Malaysia, Russia, and Vietnam; three exploratory developmental research grants in Cambodia, Haiti, and Senegal; and five multiproject research grants in China, Peru, South Africa (2), and Thailand.

In FY 2003, NIAID initiated the International Research in Infectious Diseases (IRID) Program, which consists of small grants programs specifically designed to help foreign scientists in resource-constrained countries obtain NIH funding. To date, IRID awards have been made to investigators in Africa, Eastern Europe, South America, and the South Pacific.

### Official Bilateral Programs

In addition to regular scientific channels, the United States often develops formal, bilateral scientific agreements with foreign governments or organizations at the level of the President, the Department of Health and Human Services (DHHS), the NIH, or NIAID. NIAID carries out these programs with budgeted funds unless special or supplementary funds are made available. NIAID has actively participated in bilateral programs involving Brazil, China, France, the Republic of Georgia, Germany, India, Israel, Italy, Japan, Korea, Mexico, Russia, South Africa, Vietnam, and Taiwan. Of particular interest is the U.S.–Japan Cooperative Medical Science Program (USJCMSP), which consists of committees of senior scientists and panels of experts in high-priority diseases of the Pacific Rim. Both the Joint USJCMSP Committee and

Joint Panels meet annually, alternating countries in conjunction with scientific conferences. The USJCMSP has organized annual workshops on emerging and re-emerging infectious diseases in the Pacific Basin at different sites in the region. Active priority areas are AIDS, acute respiratory infections, cholera and other bacterial enteric diseases, environmental genomics and carcinogenesis, infectious hepatitis, immunology, leprosy/tuberculosis, nutrition and metabolism, parasitic diseases, and viral diseases.

### **International Agencies and Organizations**

NIAID has joined with other organizations to enhance scientific collaborations in combating infectious diseases. Examples include the Presidential Millennium Vaccine Initiative; the Global Alliance for Vaccines and Immunization; the Multilateral Initiative on Malaria in Africa; the International Cooperative Biodiversity Groups Program; and the DHHS–State Department Biotechnology Engagement Program and the Civilian Research and Development Foundation, both of which provide

support to scientists in newly independent states of the former Soviet Union to conduct collaborative research on problems of public health importance.

NIAID staff members also participate on the scientific boards of and as consultants to the World Health Organization, the Pan American Health Organization, and the U.S. Agency for International Development.

On February 23, 2004, the first \$350 million in funding of the President's Emergency Program for AIDS Relief (PEPFAR) was made available and began reaching people in need only 2 weeks later. The second distribution of funding continued to build on prevention, treatment, and care efforts. In FY 2005, PEPFAR spent \$2.8 billion to fight global AIDS. PEPFAR countries include Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia. NIAID currently supports the work of PEPFAR in Ethiopia, Haiti, and South Africa.

## HEPATITIS C

Hepatitis C virus (HCV) has infected more than 170 million people worldwide, including 3.9 million people in the United States.<sup>35</sup> HCV continues to emerge as a serious infectious disease in the United States and worldwide. About 25,000 new U.S. infections occur each year, and liver failure resulting from HCV infection is the leading cause of liver transplants in the United States.<sup>36</sup> Before 1990, patients who received blood transfusions were vulnerable to an unknown infectious agent of liver disease then known only as non-A, non-B hepatitis. However, after being cloned and genetically sequenced more than a decade ago, HCV was identified as the cause of most of these unidentified, transfusion-related liver infections.

Fortunately, rapid improvements in HCV diagnostics, including tests that can detect both antibodies to the virus and the virus itself, have made the supply of blood and blood products in this country safe from HCV contamination. Today, injection drug users are at highest risk of infection. Sexual transmission also occurs, especially among people with multiple partners, and other transmission routes are also possible, including exposure to contaminated blood. Approximately 55 to 85 percent of infected people become chronic carriers of the virus.<sup>37</sup> However, because people with chronic HCV infection often show no overt symptoms even as their livers are being attacked by the virus, many current carriers do not know they are infected.

NIAID has aggressively expanded its HCV research program through its Framework for Progress on Hepatitis C. In collaboration with participating Institutes and Centers, NIAID developed an NIH-wide framework that incorporates the different missions of NIH into a cohesive global plan for hepatitis C research. The final plan was reviewed by outside experts and has been approved by NIH Institute and

Center Directors and the NIH Director. The plan identified the following research goals:

- Understand transmission modes to develop effective intervention strategies;
- Understand pathogenic mechanisms and disease progression to develop new treatments;
- Characterize host immune responses to infection to develop new vaccines and therapies;
- Define viral replication and recovery during therapy;
- Investigate clinical manifestations in order to develop methods to noninvasively evaluate disease state, predict outcomes, and prevent or reverse disease progression; and
- Define effective prevention and intervention strategies to improve health.

The tools needed to achieve these goals include tissue culture systems, small animal models, well-defined clinical cohorts, and research and reference reagents and tools.

NIAID supports a robust hepatitis C research portfolio that encompasses a range of critical areas, from cell culture systems to animal model development, virus replication to gene expression, crystal structure determination to rational drug development, and immune responses to vaccine development. These research activities are supported through grants to individual investigators and cooperative agreements via a network of Hepatitis C Cooperative Research Centers, in which a fusion of basic and clinical research is achieved so that laboratory observations can be clinically validated and clinical observations can be investigated at the molecular level. Through this network, NIAID supports clinical research that emphasizes studies

in special populations heavily affected by HCV such as African-Americans.

Current hepatitis C therapies include various forms of interferon and long-lasting forms of interferon (pegylated interferon), alone or in combination with the antiviral drug ribavirin. The success rates of these therapies, determined by the achievement of sustained elimination of virus, vary, depending on several factors—primarily, the genotype of the infecting virus (there are six distinct genotypes of HCV, all of which are globally distributed but with variable geographic predominance). Genotype I, the predominant strain in the United States, is the least responsive to interferon treatment, with only a 50 percent overall response rate. Also, African-Americans are considerably less responsive to therapy than are Caucasians. NIAID funds studies to understand these racial disparities in treatment responses. NIAID also supports research, new drug development, and the identification of new molecular targets for therapy, e.g., HCV polymerase, protease and helicase proteins, as well as other viral components critical for replication, such as the internal ribosome entry site (IRES).

Extramural investigators recently developed efficient HCV replication systems that can produce virus that is infectious in both human hepatocytes in cell cultures and in chimpanzees. These systems will soon close a huge gap in *in vitro* drug discovery programs supported by NIAID contracts and in the pharmaceutical industry. Information on these resources, which are accessible to both academic and corporate scientists, is available at [www.niaid.nih.gov/dmid/viral](http://www.niaid.nih.gov/dmid/viral).

Impressive advances are being made in understanding some of the mechanisms by which HCV subverts innate immunity and the adaptive immune responses to establish chronic infection. These advances are crucial to the rational design of vaccines and immunotherapies. The identification of the immune responses

that define the rare natural ability to clear acute infection spontaneously remains a major goal. This is an area of intense interest and effort for continued NIAID-supported HCV research and drug development.

Efforts are in progress to develop and test preventive and therapeutic HCV vaccines (for use in chronically infected patients). In FY 2004, NIAID concluded a phase I trial of Chiron Corporation's prototype E1E2 HCV vaccine, intended to evaluate the safety, tolerability, and immunogenicity of this vaccine candidate in healthy, uninfected human subjects. Other trials are in preparation.

The extramural program of NIAID supports a contract for the acquisition and provision of HCV research reagents, currently housed in the AIDS Research and Reference Reagent Program ([www.aidsreagent.org](http://www.aidsreagent.org)). This program is to be expanded; with the large numbers of reagents now being developed, many are expected to become reference standards for wide use in the research community, to allow uniformity and comparability of data from different laboratories and clinical research sites. Other HCV-related reagents are available through the NIH Tetramer Facility ([www.niaid.nih.gov/reposit/tetramer/index.html](http://www.niaid.nih.gov/reposit/tetramer/index.html)) and the NIAID Reference Reagent Repository ([www.kamtekinc.com/niaid.php](http://www.kamtekinc.com/niaid.php)).

NIAID also owns and maintains an annotated HCV sequence database and an HCV immunology database through a contract with the Los Alamos National Laboratories ([hcv.lanl.gov/content/hcv-db/index](http://hcv.lanl.gov/content/hcv-db/index)).

In 2002, NIAID cosponsored a Consensus Development Conference entitled "Management of Hepatitis C: 2002". The meeting was convened to provide an update to a 1997 conference on the same topic. Among the recommendations for future research in its report, the panel gave top priority to the development of reliable and reproducible HCV cultures to advance

understandings of HCV biology and mechanisms of drug resistance and aid vaccine development.<sup>38</sup> The panel also urged the establishment of a hepatitis research network that would conduct research into the natural history, prevention, and treatment of hepatitis C. In 2005, NIAID organized a workshop, “Vaccines for Hepatitis C Virus”, to discuss various issues and problems in the development of vaccines for HCV. A major outcome of the workshop was the recognition that, despite gaps in understanding protective immune responses, it is necessary to bring vaccine candidates to the fore and begin the iterative process of vaccine development and testing. A partnership initiative has since been developed to encourage and solicit the participation of private companies, in collaboration with academic institutions and with NIAID support, to produce vaccines that can be advanced to preclinical and early clinical trials within a few years.

NIAID also continues to help support the ancillary studies of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial of the National Institute of Diabetes and Digestive and Kidney Diseases. This trial is evaluating the impact of long-term therapy on disease progression, and seeks to correlate virologic parameters and immunologic responses with recovery.

Scientists in NIAID’s Division of Intramural Research are conducting research to answer key questions about HCV pathogenesis and the host immune response in order to develop an effective HCV vaccine and better hepatitis C treatments. Along the way, they are improving the tools used in hepatitis research. They are also developing critical research reagents and sharing them with researchers around the country.

For example, NIAID scientists previously collaborated with colleagues in France to demonstrate that a new *in vitro* test to detect and quantify virus neutralizing antibodies worked as well as a more cumbersome test that requires the

use of chimpanzees.<sup>39</sup> This test is now helping researchers identify the specific portions of HCV that induce protective antibodies and can be used to promote the development of an effective hepatitis C vaccine.

In 2005, NIAID scientists and their colleagues used this new method to further their studies of HCV neutralizing antibodies. Using this assay, they defined the role of neutralizing antibodies in acute and chronic HCV infections and demonstrated significant cross-genotype neutralization. The detection of high-titer neutralizing antibodies with cross-genotype reactivity has important implications for the development of vaccines and immune-based therapies against HCV.<sup>40</sup>

In addition, NIAID intramural scientists and their colleagues continued their research to develop anti-HCV immune globulin preparations—similar to those used successfully to treat hepatitis B virus infection—that might be useful in preventing or controlling HCV infections. In recent work, they studied five monoclonal antibodies derived from the bone marrow of a healthy chronic carrier of HCV who was infected more than two decades ago. This patient was shown previously to possess serum neutralizing antibodies to HCV and has been the source of well-characterized HCV. The results of the research demonstrated that one or more of these monoclonal antibodies could be useful in preventing infections by HCV belonging to genotype 1 or 2, the most medically important HCV types worldwide. The scientists’ goal is to produce these monoclonal antibodies in sufficient quantity to allow their evaluation in chimpanzees. Ultimately, such antibodies could be used to prevent recurrent HCV infection among liver transplant recipients. In HCV infection, re-infection of the transplanted liver is universal, and new therapies that enhance transplant and patient survival are sorely needed.<sup>41</sup>

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This basic research, as well as vaccine and therapeutic development, would be greatly aided by the development of a small animal model in which to study HCV and to fine-tune candidate vaccines and antibody therapies. To this end, NIAID researchers are working to determine

whether GB virus B, a monkey virus that is the closest relative of HCV, is a suitable surrogate for HCV in experimental studies. If so, the tamarin monkey could be used for *in vivo* studies and greatly reduce the need for chimpanzees for HCV research. Work in this area has been encouraging.

## IMMUNE TOLERANCE

The immune system is precisely tuned to distinguish biochemical structures that belong to the body from those that do not, allowing it to swiftly deploy a potent array of defense mechanisms whenever evidence of a foreign invasion is found. However, disorders, including autoimmune disorders, allergic diseases, and transplant rejection, are themselves caused by inappropriate immune system responses. To fight these disorders, researchers are now building on two decades of intensive basic research in immunology to develop treatments that can induce the immune system to tolerate specific antigens. Recent progress in the development of these therapies, which have the potential to be both very potent and broadly applicable, has been very encouraging.

All tolerance-induction strategies share a common goal: to selectively prevent or diminish specific harmful immune responses without disabling the immune system as a whole. In autoimmune diseases, the idea is to make the immune system tolerant to the specific, normally occurring antigens that cause it to attack the body's own organs, tissues, or cells. In asthma and allergic diseases, the goal is to prevent responses to allergens such as cockroach and house dust mite that cause or exacerbate these diseases. For transplant rejection, the goal is to selectively block immune responses directed against the foreign antigens on the graft, and thereby allow long-term graft survival without the heightened risks of infection, malignancy, and atherosclerosis associated with current immunosuppressive therapies.

NIAID supports a wide range of research programs to turn the promise of immune tolerance therapies into reality. Many of these are administrated by NIAID's Division of Allergy, Immunology, and Transplantation (DAIT), which supports basic research into the mechanisms responsible for immune tolerance, translational

research to facilitate the application of immune-tolerance approaches to human diseases, and clinical research to evaluate new therapies that can induce and maintain immune tolerance. New approaches are being investigated to

- Improve understanding of the molecular mechanisms responsible for the induction and maintenance of immune tolerance;
- Replace or improve suboptimal treatment protocols for immune-mediated diseases;
- Discover methods to prevent or reverse immune-mediated disorders for which no effective therapies are currently available;
- Create an efficient research infrastructure for the development and rapid testing of tolerogenic agents in human immune-mediated diseases; and
- Clarify mechanisms by which tolerogenic agents suppress disease.

NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Juvenile Diabetes Research Foundation International, cosponsor the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and transplant rejection. ITN conducts integrated studies on the mechanisms that underlie immune tolerance and develops markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The network has established several state-of-the-art core facilities and has supported 20 approved clinical protocols, as well as several additional studies of the immune mechanisms involved in tolerance. ITN is currently involved in the following areas of clinical research:

- Allergy
- Asthma
- Diabetes
- Islet cell, kidney, and liver transplantation
- Bone marrow transplantation
- Multiple sclerosis (MS)
- Psoriatic arthritis
- Systemic lupus erythematosus

Examples of active ITN clinical research studies include

- A phase I trial to analyze and monitor the safety of immunization with a fragment of the human insulin B chain in subjects newly diagnosed with type 1 diabetes; the hope is that this “autoimmunization” therapy will increase immune tolerance of insulin-producing cells.
- A pilot study to evaluate the safety and efficacy of a treatment regimen to induce tolerance in kidney transplant recipients. In this study, patients will receive low-dose steroid-free immunosuppression, two donor stem cell infusions, and an antibody called Campath-1H, which selectively eliminates immune-system T cells involved in organ rejection. Treatment will be withdrawn after 1 year and patients followed to see if long-term tolerance has been achieved.
- A phase I study in 16 patients with relapsing-remitting multiple sclerosis (MS) to assess the safety of one dose of CTLA4-IgG4m, an antibody that might block a pathway that allows the immune system to attack nervous system tissue.
- A phase II multicenter trial to evaluate the lipid-lowering drug atorvastatin in patients at high risk of developing MS.

Tolerance assays—tests and procedures to monitor patient responses to tolerance therapies—are critically needed to better evaluate tolerance-inducing therapies during and after clinical trials. ITN has therefore established a set of core laboratories to develop assays for the induction, maintenance, or loss of immune tolerance. These core facilities carry out microarray analyses of gene expression, develop analytic tools for clinical and scientific datasets from ITN-sponsored trials, and conduct enzyme-linked immunospot (ELISPOT) assay analyses of protein expression and cellular assays for T cell reactivity.

Examples of current ITN efforts to develop mechanistic assays include development of antigen-specific assays for donor-specific tolerance in kidney transplant recipients, cytokine production in children with preclinical and clinical type 1 diabetes, and identification and mechanistic investigations of tolerant kidney transplant patients. More information on ITN’s mission and research is available at [www.immunetolerance.org](http://www.immunetolerance.org).

In collaboration with NIDDK, DAIT supports the Nonhuman Primate Transplant Tolerance Cooperative Study Group. The goal of this program is to evaluate the safety and efficacy of novel tolerogenic regimens in preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. In FY 2005, the program expanded the scope of transplantation models to include nonhuman primate models of heart and lung transplantation, and to provide an opportunity for critical preclinical research to complement NIAID-supported transplantation clinical trials. The program’s previous expansion allowed the sharing of valuable resources and facilitated the development of new collaborations. To accelerate research conducted through this program, DAIT

maintains breeding colonies of specific pathogen-free rhesus and cynomolgus macaques.

Other DAIT-supported research programs that include studies on immune tolerance are the Autoimmunity Centers of Excellence, Innovative Grants on Immune Tolerance, and program projects in basic biology, basic immunology, and transplantation tolerance. The goals of these projects are to (1) determine the molecular

mechanisms by which cells of the immune system are rendered unresponsive, (2) develop experimental models of tolerance induction, and (3) evaluate tolerance induction strategies in animal models of transplantation or autoimmune diseases. The knowledge gained from these program projects will accelerate the development of clinical strategies for tolerance induction in immune-mediated diseases.

## MALARIA

Malaria, a serious disease caused by parasites of the genus *Plasmodium* and transmitted by mosquitoes, continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Globally, malaria causes more than 1 million deaths each year and continues to be the most important tropical parasitic disease in terms of annual mortality.<sup>42</sup> Approximately 80 percent of malaria deaths worldwide occur in Africa south of the Sahara, with the majority of deaths occurring in children aged 5 years and younger.<sup>43</sup> Unfortunately, malaria parasites have developed a variety of mechanisms to resist the action of antimalarial drugs and to evade host immune responses, and the mosquitoes responsible for transmission of malaria parasites have similarly developed resistance to insecticides. Together, these factors make the sustained control of malaria technically very challenging.

Malaria research at the NIH dates back to the 1930s, when malaria was still a major public health problem in the United States. NIAID maintains a broad malaria research portfolio that includes parasite biology, pathogenesis, drug development, vaccine development, epidemiology, and vector biology. NIAID-funded malaria research is conducted by scientists at institutions throughout the United States, including NIAID intramural laboratories, and overseas.

NIAID's intramural malaria vaccine research program is centered in the Malaria Vaccine Development Branch (MVDB). The MVDB collaborates with investigators within the United States and throughout the world, as well as with the extramural NIH malaria program and a variety of funding organizations such as the U.S. Agency for International Development and the Malaria Vaccine Initiative at the Program for Appropriate Technology in Health (PATH). The MVDB has produced multiple vaccine components using the quality control practices required for manufacturing clinical materials.



**Malaria Vaccine.** First volunteer in NIAID-supported malaria vaccine trial in Mali.

Two of these have been combined into a vaccine called AMA1-C1, which was well tolerated in a phase I trial in U.S. adults and further tested in a phase I study in adults in Mali, marking the first time that MVDB products have been tested in a malaria endemic area. MVDB researchers are working to improve the immunogenicity of this formulation and to broaden the reactivity of anti-AMA1 antibody response. In addition, they have completed the preclinical studies for two other vaccine candidates and have initiated a phase I clinical trial in U.S. adults as a prelude to anticipated future studies in an endemic area in African children who desperately need a malarial vaccine to reduce disease and death. A vaccine trial for efficacy will be performed in African children, the target population who most need the vaccine. The MVDB is also developing vaccines aimed at eliminating *Plasmodium falciparum* and *Plasmodium vivax* from regions of Asia and Latin America.

Intramural investigators also are conducting basic studies aimed at providing fundamental biological information for the development of diagnostics, therapeutics, and other control measures against the disease. For example, Division of Intramural Research scientists are using the malaria parasite genome databases and microarray analysis to identify genes that might be involved in drug resistance and parasite sexual development.

Identifying these genes is an important step in developing measures to interrupt parasite transmission, and will provide critical information for drug and vaccine development.

In 2005, NIAID researchers advanced understanding of the factors that affect the severity of malaria through their discovery of the mechanism by which hemoglobin C protects children from severe and fatal complications of *P. falciparum* malaria. Along with a team of international collaborators, they found that hemoglobin C alters red blood cells so that the malaria parasites have trouble placing a protein called PfEMP-1 in knob-like protrusions at the cell surface. This makes the cells less able to adhere to blood vessels, which causes the inflammation and circulatory obstruction seen in severe disease. Other hemoglobin variants, such as the sickle-cell mutation, might protect against malaria by a similar mechanism. These findings suggest that interventions affecting the display of this protein could reduce the impact of malaria.

Through its extramural malaria research program, NIAID also supports extensive research on malaria vaccines conducted by researchers from academia and industry. The Institute currently funds multiple studies aimed at developing vaccines against different stages of the malaria parasite and has conducted clinical trials of the most promising candidates in the United States and abroad. These research efforts represent a critical component of NIAID's Research Plan for Malaria Vaccine Development, which is designed to accelerate research leading to the development of malaria vaccines. Under a contract with Science Applications International Corporation, NIAID established a capability to undertake targeted research essential to translating basic research concepts into prototype vaccine products for clinical evaluation. Recent activities included process development for production of novel candidate vaccines, production and qualification of critical reagents for quality control of new candidate vaccines, and preclinical safety

evaluation of promising candidate vaccines prior to entry into clinical trials. Reagents were also provided to the Malaria Research and Reference Reagent Resource, which will make them available to the international malaria research community.

NIAID has undertaken a phase I trial of a novel candidate malaria vaccine at the University of Maryland Center for Vaccine Development. This vaccine was developed with grant support from the Small Business Innovation Research Program administered at NIAID, with additional support and collaboration from the Malaria Vaccine Initiative at PATH. Results of this trial are expected to be available late 2006. Additional clinical trials of promising vaccine candidates are planned through NIAID's Vaccine and Treatment Evaluation Units.

A key component of NIAID's Research Plan for Malaria Vaccine Development has been the establishment of research centers in malaria-endemic areas that can support epidemiological and clinical research relevant to malaria, as well as conduct clinical trials. In collaboration with the Walter Reed Army Institute of Research, the University of Maryland Center for Vaccine Development, and the University of Bamako (in Mali), NIAID has now completed two trials of novel candidate malaria vaccines in Mali. Additional clinical trials of candidate malaria vaccines are scheduled for Mali and Ghana in 2006.

Identification, validation, and evaluation of new antimalarial therapies remain NIAID priority activities. In 2004, NIAID issued a renewal of the Tropical Diseases Research Units (TDRU) program. The objective of the TDRU program is to support translational research leading to the discovery and preclinical development of new drugs and vector control methods to reduce or eliminate morbidity and mortality resulting from parasitic infection. One of the three new awards made under this program

focuses on development of novel antimalarials. The Challenge Grants and Partnerships Program has funded requests for applications for collaborations with private companies for the development of new compounds and strategies for malaria treatment and mosquito control. These initiatives currently support studies aimed at the screening and validation of novel classes of anti-mosquito candidates, exploring the use of larval control strategies in certain areas in Africa, mitigating insecticide resistance, and developing new environmentally safe insecticides to kill mosquitoes. NIAID also supported a phase I clinical trial of a chloroquine analog effective against chloroquine resistant *P. falciparum*, as well as investigator-initiated research on preclinical development and evaluation of novel compounds. The Institute also supports preclinical and clinical studies of combination therapies for malaria, especially those including artesunate, and works with other groups (such as the U.S. Food and Drug Administration and the nonprofit organization, Medicines for Malaria Venture) to develop a consensus on the design of clinical trials of artemisinin-containing antimalarial drug regimens.

Clinical research capacity continues to be strengthened in overseas sites in Africa with support through the “Malaria Vaccines: Clinical Research and Trial Sites in Endemic Areas” contract and through grants awarded through the International Collaborations in Infectious Disease Research program. Research staff members continue to participate in training in epidemiology, bioethics, good clinical practice, good laboratory practice, and financial

management. Clinical facilities, research and clinical safety laboratories, and satellite Internet connectivity have been established or expanded.

NIAID also continues to participate in the Federal Malaria Vaccine Coordinating Committee and provides support to the Multilateral Initiative on Malaria and the World Health Organization Special Programme for Research and Training in Tropical Diseases Task Force to advance malaria research and research capacity-strengthening activities at African institutions. Moreover, NIAID participates in the Malaria Vaccine Advisory Committee established at the World Health Organization Initiative for Vaccine Research and in the External Scientific Advisory Committee of the Medicines for Malaria Venture, a public-private partnership that fosters the accelerated development of new antimalarial compounds. In addition, NIAID has worked with the European Commission, the European Malaria Vaccine Initiative, and the European-Developing Countries Clinical Trial Partnership to coordinate product development and clinical trial activities in vaccines and drugs.

In addition to the targeted activities listed above, malaria-related research and training activities are supported under a number of other programs, such as the TDRUs, International Centers for Tropical Diseases Research Network, U.S.–Japan Cooperative Medical Science Program, Indo–U.S. Vaccine Action Program, and Clinical Research and Training Opportunities. Additional information is available at [www.niaid.nih.gov/ictdr/tdru.htm](http://www.niaid.nih.gov/ictdr/tdru.htm).

## MINORITY AND WOMEN'S HEALTH

NIAID's Office of Special Populations and Research Training (OSPRT) provides oversight and coordination to the Institute's activities in the area of minorities' and women's health, and research training. OSPRT has provided the National Center for Minority Health and Health Disparities with benchmarks on progress made to initiatives contained in the NIAID "Strategic Plan for Addressing Health Disparities: FY 2002–2006" (available at [www.niaid.nih.gov/healthdisparities/NIAID\\_HD\\_Plan\\_Final.pdf](http://www.niaid.nih.gov/healthdisparities/NIAID_HD_Plan_Final.pdf)). The plan lists three goals: (1) to conduct research to identify and address health disparities among various populations affected by infectious and immunologic diseases, (2) to increase the number of minority scientists and grantees, and (3) to improve education and outreach activities for the transfer of health information to these populations. NIAID continues to prioritize basic, clinical, and epidemiologic research on the health problems of minorities and women; efforts to increase participation of minority scientists in its research programs; and outreach activities designed to communicate research developments to these populations.

These efforts are translated into a scientific portfolio of research programs on diseases that disproportionately impact minorities' and women's health.

### Minority and Women's Health Programs

NIAID's programmatic research agenda for minorities' and women's health includes immune-mediated diseases, infectious agents, AIDS, vaccine prevention, and therapeutic interventions, in an effort to alleviate the many risk factors in minorities and women health. The Institute conducts basic and clinical research, either through its intramural laboratories or through federally-funded extramural mechanisms, on a broad spectrum of these diseases. Additionally,

the Institute collaborates with other organizations to address health disparities in these populations.

**Asthma.** Asthma is a chronic disease affecting more than 20 million Americans. It disproportionately affects minorities, particularly African-American and Hispanic children residing in inner cities. Results from the Inner-City Asthma Study, cosponsored by the National Institute of Environmental Health Studies, indicated that physician education and an extensive environmental intervention successfully reduced allergen levels in the homes of inner-city children with asthma. This reduction resulted in an improvement in asthma morbidity, measured by decreases in asthma symptoms, number of hospitalizations, and number of unscheduled physician visits for asthma. The reduction continued 1 year post-intervention. The physician feedback intervention resulted in a 20 percent decrease in unscheduled emergency room or clinic visits for poorly controlled asthma.<sup>44</sup> These findings could lead to significantly improved health for inner-city children with asthma and reduce the high medical, economic, and social costs associated with this disease.

**Autoimmune diseases.** Autoimmune diseases are those in which the immune system mistakenly attacks the body's own cells, tissues, and organs. Autoimmune diseases affect an estimated 5 to 8 percent of the U.S. population, approximately 14 to 24 million people. Several of these diseases disproportionately affect women and minority populations. For example, in some autoimmune diseases, including thyroiditis, scleroderma, systemic lupus erythematosus (SLE), and Sjögren's syndrome, females represent 85 percent or more of patients. Ninety percent of the nearly 2 million Americans diagnosed with (or suspected of having) SLE are women. SLE damages multiple tissues and organs and can affect muscles, skin, joints, and kidneys, as well as the brain and nerves. In other diseases such as multiple sclerosis, myasthenia gravis, and inflammatory bowel diseases, the disparity

is smaller, with females representing 55 to 70 percent of patients. The reasons for these gender-based variations are not known.

NIAID supports a broad range of basic and clinical research programs in autoimmunity, including the Autoimmunity Centers of Excellence, the Autoimmune Diseases Prevention Centers, and multidisciplinary research on gender-based differences in immune responses. In FY 2005, the Prevention Centers supported 22 pilot projects to test innovative prevention approaches or methods to measure biomarkers of autoimmune disease progression. In FY 2005, NIAID began conducting clinical trials through the Stem Cell Transplantation for Autoimmune Diseases Consortium to assess the efficacy of hematopoietic stem cell transplantation to treat severe multiple sclerosis, SLE, and scleroderma. The consortium also will conduct studies of the underlying immune mechanisms of these diseases. NIAID chairs the trans-NIH Autoimmune Diseases Coordinating Committee (ADCC), which submitted its Research Plan to Congress in December 2002. The ADCC submitted its third report to Congress in March 2005; it summarized FY 2003 NIH accomplishments and activities in autoimmune diseases research. For the ADCC Research Plan, see [www.niaid.nih.gov/publications/pdf/ADCCFinal.pdf](http://www.niaid.nih.gov/publications/pdf/ADCCFinal.pdf).

Collaborations among NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Juvenile Diabetes Research Foundation International established the Immune Tolerance Network (ITN), an international consortium dedicated to the clinical evaluation of novel, tolerogenic approaches for the treatment of autoimmune diseases, asthma and allergic diseases, and the prevention of graft rejection. ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. ITN includes more than 80 basic and clinical scientists and physicians at more

than 40 institutions in the United States, Canada, Europe, and Australia. For more information about the ITN, see [www.immunetolerance.org](http://www.immunetolerance.org).

**Hepatitis C.** Hepatitis C virus (HCV) infection is the most common chronic bloodborne viral infection in the United States. An estimated 3.9 million (1.8 percent) Americans have been infected with HCV, and 2.7 million of them are chronically infected. New infections in the United States continue at the rate of approximately 30,000 cases per year.<sup>45</sup> HCV disproportionately affects minority populations, particularly African-Americans and Hispanics. Moreover, available treatments for HCV tend to be less effective for African-Americans than for other populations.<sup>46</sup>

To investigate this issue, NIAID is supporting a study to determine whether there are specific genetic and molecular factors that cause African-American patients to respond poorly to the standard interferon and ribavirin therapy used for hepatitis C that seems to be effective in White populations. Understanding the reasons for differential drug responses among these populations could lead to the development of new drugs to treat HCV. In particular, NIAID supports the Hepatitis C Cooperative Research Centers (CRC) network, which unites basic and clinical researchers investigating HCV infection and the disease process to identify new and better means of prevention and treatment.

One Hepatitis C CRC is conducting an epidemiological study of the relationships between HCV replication, evolution, and disease progression in Alaska Natives. This well-defined and well-monitored study could provide important information about the natural history of hepatitis C and affect the future treatment of hepatitis C worldwide.

**HIV/AIDS.** HIV/AIDS continues to disproportionately affect minorities. Racial and ethnic minority populations in the United States, primarily African-Americans and Hispanics,

constitute 58 percent of the more than 900,000 cases of AIDS reported to the Centers for Disease Control and Prevention (CDC) since the epidemic began in 1981. African-Americans make up almost 40 percent of all AIDS cases reported in the United States, yet according to the U.S. Census Bureau, they comprise only 13 percent of the U.S. population. Hispanics represent 19 percent of all AIDS cases and are approximately 14 percent of the U.S. population. Of the new AIDS cases reported in 2004, 49 percent were among African-Americans, 20 percent among Hispanics, 28.3 percent among Whites, and 1.7 percent among American Indians/Alaska Natives and Asian Americans/Pacific Islanders. Among women, African-Americans and Hispanics account for 83 percent of AIDS cases; among men, African-Americans and Hispanics account for 64 percent of cases. Injection drug use is a major factor in the spread of HIV in minority communities. Other factors contributing to the spread of HIV/AIDS in these communities include male-to-male sexual contact and, increasingly, heterosexual transmission.<sup>47</sup>

HIV/AIDS also continues to increase among women. In 2004, the Joint United Nations Programme on HIV/AIDS estimated that 40.3 million people were living with HIV/AIDS worldwide, with women accounting for nearly 50 percent of all cases.<sup>48</sup> In the United States, as of December 2004, women accounted for more than 18 percent (178,463) of the cumulative estimated number of 944,306 AIDS cases reported among adults and adolescents. In recent years, the incidence of AIDS has increased more rapidly among women than men. The proportion of new AIDS cases among women more than tripled from 1985 to 2002, from 7 percent to 26 percent. Almost 56 percent of HIV-infected women in the United States acquired HIV through heterosexual contact with HIV-infected men, and 40.7 percent through injection drug use. Also, HIV infection disproportionately affects minority women. Seventy-nine percent of HIV-infected women are African-American and/or of Hispanic ethnicity,

compared with only 58.5 percent of HIV-infected men.<sup>49</sup>

Worldwide, women are at an increased risk of acquiring HIV due to substantial mucosal exposure to seminal fluids, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners. Women also face gender-specific manifestations of HIV disease such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, severe herpes infections, and gender-specific abnormalities related to infection with human papillomavirus and vulvar and vaginal carcinomas.

Drug metabolism also differs in women and men, potentially resulting in differential responses to antiretroviral therapy and an increased incidence of drug toxicities in women. Frequently, women with HIV infections have difficulty accessing health care, and carry a large burden of caring for children and other family members who might also be HIV-infected. They often lack social support and face other challenges that could interfere with their ability to adhere to treatment regimens. In light of this, NIAID supports clinical research to investigate gender-specific differences in HIV disease progression, complications, and treatment responses. These studies are being conducted by the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Community Programs for Clinical Research on AIDS (CPCRA). For example, several studies have been initiated through the AACTG to examine the pharmacokinetics of contraceptives in the setting of highly active antiretroviral therapy (HAART); use of antiretroviral therapy in pregnancy; gender differences in responses to HAART among treatment-naïve patients; toxicities and complications of different treatment regimens for HIV and HIV co-infections, such as human papillomavirus; metabolic complications of HAART; and postpartum changes in

immunologic responses. For more information about the AACTG, visit [www.aactg.org](http://www.aactg.org).

NIAID also supports investigations of the course of HIV/AIDS disease in women and men in the United States through two epidemiological cohorts, the Women's Interagency HIV study (WIHS) and the Multicenter AIDS Cohort Study (MACS). The WIHS is a cohort of both HIV-infected and uninfected women, while the MACS is a prospective, longitudinal study of HIV disease in homosexual and bisexual men. Studies of these cohorts have repeatedly made major contributions to understanding how HIV is spread, how the disease progresses, and how it can best be treated. In 2003, the WIHS and MACS expanded their study groups by 60 percent to increase the number of minority participants. Studies of the expanded cohorts focus on contemporary questions regarding HIV infection and treatment. For more information about WIHS and MACS, visit <http://statepiaps.jhsph.edu/wihs> and <http://statepi.jhsph.edu/mac/mac.html>.

WIHS researchers have published more than 250 peer-reviewed articles covering a wide scope of scientific research including the natural history of HIV infection; the impact of opportunistic infections and co-infections; the value of HIV viral load and CD4+ cell counts as markers of the success of HAART; clinical outcomes of HAART therapy; the identification of biological, psychosocial and behavioral risk factors; the impact of aging and hormonal factors; the study of HIV-associated malignancies, particularly cervical cancer caused by the human papillomavirus; the analysis of gender differences in HIV disease; and the development of novel methods for analyses of cohort data. In addition, the WIHS has provided an invaluable repository of clinical specimens and accompanying demographic and epidemiologic data to be used for retrospective hypothesis testing. Currently, the WIHS is evaluating the cardiovascular manifestations of HIV among women.

NIAID is also cosponsoring a new program, the Pediatric HIV/AIDS Cohort Study (PHACS), with the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, and the National Institute of Mental Health. The objective of PHACS is to address continuing critical research questions on the clinical course of perinatally acquired HIV infection in adolescents and the consequences of fetal and neonatal exposure to antiretroviral chemotherapy in a representative cohort of children from the United States. The PHACS Leadership Group was funded this year for specific protocols to begin in FY 2006.

Mother-to-child transmission (MTCT) of HIV can occur during pregnancy, childbirth, or through breastfeeding and accounts for more than 90 percent of all cases of childhood HIV infection, especially in countries where effective antiretroviral drugs are not available. As more women of childbearing age become infected, the number of children infected with HIV also is expected to rise.<sup>50</sup> Efforts to prevent MTCT by targeting both the infant and the mother are being examined by the HIV Prevention Trials Network (HPTN) and the PACTG. Data from a NIAID-funded study that began in November 1997 in Uganda showed that the initial benefit to infants, who, along with their mothers, received one dose of nevirapine, was sustained by the group of children until they reached age 18 months. These findings indicate that short-course nevirapine effectively and safely reduces MTCT of HIV and, because of its low cost and ease of administration, provides an important alternative in resource-poor developing countries.

The HPTN also conducts clinical trials of non-vaccine HIV prevention strategies, including topical microbicides. A topical microbicide is a preparation (e.g., gel, cream, or foam) that is applied to the vagina or rectum to inactivate or inhibit pathogens, including HIV, which can be transmitted during sexual intercourse. For more on

microbicides, see page 126. For more information about the HPTN, visit [www.hptn.org](http://www.hptn.org).

NIAID's HIV Vaccine Trials Network (HVTN) is an international network dedicated to developing and testing candidate HIV vaccines in all phases of clinical trials. Both HVTN and HPTN have initiated community outreach programs to educate people about HIV vaccine and prevention research and to encourage participation in clinical trials. Through these outreach activities, HVTN and HPTN researchers aim to enroll a diverse population in their clinical trials, including women and minorities. For more information about the HVTN, visit [www.hvtn.org](http://www.hvtn.org).

One of the greatest challenges facing HIV/AIDS researchers today is the recruitment and retention of minorities and women for clinical trials. As the epidemic continues to expand in minority communities, inclusion of these individuals in clinical trials is particularly urgent to ensure that the results of research are applicable to all populations affected by the disease. In October 2003, NIAID hosted a conference, "Increasing Diversity in Clinical Trials: Best Practices", to explore the most effective strategies for recruiting minorities and women. For more information about the conference, see: [www.niaid.nih.gov/healthdisparities/hdsymposium/proceedings2](http://www.niaid.nih.gov/healthdisparities/hdsymposium/proceedings2). In 2003, to address this issue directly, NIAID released a program announcement, "Enrolling Women and Minorities in HIV/AIDS Research Trials," to fund innovative approaches to reach, enroll, and retain women and racial/ethnic minorities in HIV/AIDS research trials in the United States. The initiative supports projects to increase the number of women and minorities who participate in clinical trials for HIV/AIDS relative to the incidence data, and is designed to advance the body of scientific knowledge to improve the diagnosis, treatment, and development of preventive strategies in women and minorities. Additionally, each of NIAID's large, multicenter therapeutic clinical trials

networks, i.e., AACTG, PACTG, and CPCRA, strives to ensure enrollment of a sufficient proportion of minority subjects.

NIAID, through its Division of AIDS, is actively involved in educating the public about HIV vaccine research. Targeting at-risk populations, in particular African-Americans, Hispanics, and men who have sex with men, NIAID is implementing a national education campaign to increase awareness of and support for HIV vaccine research. Specifically, the campaign is designed to (a) increase awareness about the urgent need for an HIV vaccine within communities most affected by HIV/AIDS; (b) create a supportive environment for current and future HIV vaccine trial volunteers; and (c) improve the public's perceptions and attitudes towards HIV vaccine research.

An additional challenge is the recruitment of underrepresented minority investigators to AIDS and AIDS-related clinical and basic research disciplines. To address this challenge, NIAID supports a comprehensive portfolio of biomedical and behavioral research aimed at preventing and treating HIV disease in minority communities, training minority investigators, and fostering infrastructure development. NIAID continues to co-fund, with the National Center for Research Resources, the Research Centers in Minority Institutions (RCMIs) program by providing support for HIV/AIDS research pilot projects as well as infrastructure development at RCMIs. In FY 2005, NIAID awarded \$2.4 million to support projects at four institutions for research in diverse areas such as vaccine development, drug development, opportunistic infections, immunology, and a Comprehensive Center for Health Disparities.

In addition, in FY 2005, NIAID awarded grant supplements under the Research Supplement to Promote Diversity in Health-Related Research Program, formerly known as the Research Supplements for Underrepresented

Minorities (RSUM) program. The purpose of this program is to attract underrepresented minority investigators into biomedical and behavioral research. The supplements are made to NIAID-funded grantees to recruit and support investigators interested in a particular area of scientific research. The awards are made on behalf of postdoctoral candidates, graduate students, faculty members, undergraduates, and reentry and disabled investigators. Several of the NIAID-sponsored Centers for AIDS Research also have a significant commitment to educating and training minority investigators and providing outreach to minority communities.

**Sexually Transmitted Infections.** Sexually transmitted infections (STIs) are critical global and national health priorities because of their devastating impact on minorities, women, and infants and their inter-relationship with HIV/AIDS. STIs are widespread, with 19 million new cases estimated to occur each year in the United States.<sup>51</sup> Several STIs, including genital herpes, gonorrhea, chlamydia, and syphilis, have higher incidences among minorities than among Whites in the United States.<sup>52</sup>

Symptoms of STIs in women can be minor or nonspecific, especially in the early stages, and are often not diagnosed until late in the disease. STIs that occur during pregnancy can affect the fetus or newborn. About one-quarter to one-half of women infected with an STI during pregnancy give birth to either premature or low birthweight infants. In about one-third to two-thirds of these pregnancies, the infection is passed to the infant and can cause permanent disabilities. Chlamydia, gonorrhea, and other infections of a woman's upper reproductive tract also can complicate pregnancy.

**Chlamydia** is the most commonly reported sexually transmitted bacterial disease in the United States. In 2004, more than 900,000 chlamydia infections were reported to the CDC. In women, chlamydia infections can cause pelvic

inflammatory disease, which is a major cause of infertility, ectopic pregnancy, and chronic pelvic pain. The rate of reported infection with *Chlamydia trachomatis* is over three times greater in women than men, and is particularly high in adolescent women. In 2004, the rate of chlamydia among African-American females in the United States was more than seven and a half times higher than the rate among white females (1,722.3 and 226.6 per 100,000, respectively). The chlamydia rate in African-American males was 11 times higher than that in White males (645.2 and 57.3 per 100,000 respectively).<sup>53</sup> NIAID-supported researchers conducted a randomized clinical trial that examined whether expedited treatment could reduce rates of recurrent or persistent gonorrhea and chlamydial infections among women and heterosexual men. Results of this study showed that expedited treatment of sex partners increased the proportion of partners who received the treatment and decreased persistent and recurrent gonorrhea and chlamydial infection among the study participants.

**Gonorrhea** is the second most commonly reported notifiable disease in the United States. Infections due to *Neisseria gonorrhoeae* are a major cause of pelvic inflammatory disease. Between 2000 and 2004, overall gonorrhea rates declined by 15.2 percent. African-American women between the ages of 15 to 19 had the highest rates among all groups.<sup>54</sup>

**Genital herpes** affects at least 45 million people in the United States. About one in five adolescents and adults in the United States has genital herpes, but most are unaware they have the virus. Although most genital herpes cases present no symptoms, asymptomatic individuals can transmit herpes simplex virus (HSV type 1 or 2) to others, and a pregnant woman infected with HSV can transmit the virus to her baby.<sup>55</sup> NIAID is investigating treatments for herpes, including antiviral drugs and monoclonal antibodies, as well as studies to assess the role of antiviral suppressive therapy and vaccination in decreasing herpes

transmission. In FY 2003, NIAID launched a pivotal phase III double-blind clinical efficacy trial of Herpevac, an investigational vaccine for the prevention of genital herpes in women ages 18 to 30. This trial, called the Herpevac Trial for Women, is being conducted at more than 35 clinical sites across the United States as a public-private partnership between NIAID and GlaxoSmithKline. For more information about the Herpevac Trial for Women, see: [www.niaid.nih.gov/dmid/stds/herpevac/default.htm](http://www.niaid.nih.gov/dmid/stds/herpevac/default.htm).

**Group B Streptococcus (GBS)** is another infectious bacterium that can cause disease in women. This bacterium can produce harmful infections in women during pregnancy and can cause infections in newborns as a result of being passed from mother to child during labor and delivery. When these infections occur in newborns, they can be life-threatening. Although women often receive antibiotics during labor to prevent GBS infection in their babies, GBS infections remain a leading cause of neonatal disease.

NIAID is currently supporting a GBS vaccine research study called the Streptococcal Prevention in Non-Pregnant Women Study to determine whether a single vaccination with an investigational GBS type III vaccine can prevent non-pregnant women from acquiring GBS type III bacteria in their reproductive tract. There are several types of GBS; type III is being studied because it is common in newborn infections.

**Syphilis** is caused by *Treponema pallidum*, a bacterium that is most commonly transmitted through sexual activity. It is possible for pregnant women with the disease to pass the bacterium to their unborn children, in whom it can cause serious mental and physical disorders. Although the number of cases of syphilis is declining in the United States, in 2004, young women 20 to 24 years of age and men 35 to 39 years of age had the highest incidence of syphilis.<sup>56</sup> In 2004, the rate of primary and secondary syphilis among

African-Americans was 5.6 times higher than the rate among Whites.<sup>57</sup> The NIAID-supported Sexually Transmitted Disease (STD) Clinical Trials Unit is currently conducting a randomized phase III trial to evaluate the equivalency of oral azithromycin versus injectable benzathine penicillin for treatment of primary syphilis. If successful, this could provide an additional antimicrobial strategy for treatment of this difficult disease.

**Trichomoniasis** is a common sexually transmitted infection in the United States that affects both men and women, although symptoms are more common in women. Trichomoniasis is caused by a single-celled protozoan parasite called *Trichomonas vaginalis*. There are an estimated of 7.4 million new cases a year in both men and women in the United States. Epidemiologic studies suggest trichomoniasis is 1.5 to 4.0 times more common among African-Americans than other racial/ethnic groups.<sup>58</sup> The NIAID-supported STD Clinical Trials Unit recently completed a multisite clinical study to determine the concordance of trichomoniasis between male and female partners.

NIAID has created an extensive infrastructure for conducting basic and applied research on STIs, including the STI Cooperative Research Centers, the STI Clinical Trials Unit, and the Topical Microbicides Program. These activities are part of an overall Institute effort to initiate and support a variety of research projects that focus on (1) developing vaccines, topical microbicides, and treatments for the microbes that cause STIs; (2) developing better and more rapid diagnostics; (3) sequencing the genomes of sexually transmitted pathogens; and (4) understanding the long-term health impact of sexually transmitted pathogens in various populations. For more information about NIAID research on sexually transmitted diseases, see: [www.niaid.nih.gov/dmid/stds](http://www.niaid.nih.gov/dmid/stds).

In addition, NIAID supports several clinical and epidemiological studies that are focused on

STIs in minority populations. The goals of these studies include identifying risk factors for STIs in minority populations, examining the relationship of STIs with infertility and pregnancy outcomes, and evaluating the effectiveness of prevention and control strategies in minority communities.

NIAID also supports training of minority scientists in the area of STI research. Through a collaborative training program with the Sexually Transmitted Disease CRCs, NIAID supports a research program with second-year medical students from Howard University in Washington, DC. This program provides students with a 10-week STI research experience at the STI CRCs, with the long-term objective of encouraging young minority physicians to pursue careers in STI research.

**Transplantation.** Transplantation treatment and effectiveness represent a key health disparity for African-Americans, who are at increased risk for end-stage organ failure and the need for a transplant. Despite a disproportionate representation on organ transplant waiting lists (27.2 percent of the total and 35 percent of kidney waiting list candidates), African-Americans comprised only 18 percent of transplant recipients in 2004. In contrast to these disparities, African-Americans, who make up approximately 12 percent of the U.S. population, accounted for 14.1 percent of deceased organ donors in 2004. (For more information about data on transplantation, see the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients Annual report available at: <http://www.optn.org/AR2005/default.htm>.)

For reasons that are not well understood, African-Americans experience lower survival rates after transplantation and higher incidences of acute graft rejection and long-term immunosuppression-related adverse effects than do Whites. These disparities could be related to genetic factors, immunological

factors, differences in drug pharmacokinetics, access to health care, socioeconomic factors, and medical noncompliance. To clarify the genetic factors that result in variable graft survival among populations, NIAID and the NIDDK launched the Genomics of Transplantation Cooperative Research Program in FY 2004. Researchers in this program are examining genetic polymorphisms and gene expression patterns to understand and predict transplant outcomes in diverse populations. The program will be expanded in FY 2006 with the long-term goal of understanding the genetic basis of immune-mediated graft rejection and differences in transplant outcomes. This information will provide a rational basis for the development of more effective treatment and prevention strategies to improve long-term graft survival and quality of life for transplant recipients.

For kidney transplantation, matching of histocompatibility antigens (proteins that are the major targets of immune-mediated graft rejection) between donors and recipients is a consideration in prioritizing the distribution of organs. Because of racial or ethnic differences in the frequency of alleles (variants of a gene) at human leukocyte antigen (HLA) loci, African-Americans are less likely to find a good match in the donor kidney pool than are candidates from other racial or ethnic groups, and the rate of graft failure is proportional to the level of mismatching.<sup>59</sup> These findings also apply to bone marrow transplantation, where HLA mismatching increases the risk of graft failure and graft versus host disease.<sup>60</sup> To increase knowledge of HLA diversity and improve donor-recipient matching, NIAID supports research to identify new HLA alleles in distinct racial and ethnic groups. NIAID-supported researchers have discovered 13 new HLA alleles in African-Americans, 3 new alleles in Native Alaskan Yup'ik, and 2 new alleles in Lakota Sioux. In addition to facilitating improved donor-recipient matching in organ and hematopoietic stem cell transplantation, this research could provide

additional insights into the origin and diversity of humans. For more information about policies related to matching organ donors and recipients, see: [www.optn.org/policiesAndBylaws/policies.asp](http://www.optn.org/policiesAndBylaws/policies.asp).

In FY 2005, NIAID, with cosponsorship from the National Institute of Neurological Diseases and Stroke, awarded five research cooperative agreements under the new HLA Region Genetics in Immune-Mediated Diseases program. The objectives of this program are to define the association between HLA region genes or genetic markers and immune-mediated diseases, including risk and severity of disease and organ and cell transplantation outcomes.

**Tuberculosis.** Tuberculosis (TB), which is caused by the bacterium *Mycobacterium tuberculosis* (*M. tb*), is one of the leading causes of illness and death in the world and kills more people than AIDS and malaria combined. The World Health Organization estimates that approximately one-third of the world's population is infected with *M.tb*. Approximately 8 million new TB cases occur annually, and 2 million people die each year from TB.<sup>61</sup>

TB also remains a public health concern in the United States. The CDC estimated that, in 2005, 5 to 10 percent of the U.S. population (14 to 28 million persons) was infected with TB, and more than 14,000 new TB cases occurred in the 50 States and the District of Columbia. The disease persists disproportionately among racial/ethnic minority populations in the United States. During 2005, the TB rate among foreign-born persons was 8.7 percent times that of U.S.-born persons. The TB rates among Hispanics and African-Americans were 7.3 and 8.3 times higher than among Whites, respectively.<sup>62</sup> Combined factors such as urban poverty, high HIV infection rates, and the effects of household crowding might contribute to the disproportionate impact of TB on minorities. Also, the rise of multidrug-resistant strains of TB and co-infection with HIV

has further extended the impact of TB in the United States and around the world.

NIAID is helping to fight TB in all populations, domestically and globally, by developing promising strategies for disease control and prevention. The NIAID TB research agenda supports studies aimed at better understanding the pathogenesis and human immune response to TB and developing improved diagnostics, more effective vaccines, and novel medicines. More than 100 candidate vaccines have been screened for protective efficacy, new drugs are being examined that might lead to shorter antibiotic treatment, and innovative programs have been developed that promote international collaboration among investigators.

One such program is the Tuberculosis Research Unit (TBRU), established through a contract with Case Western Reserve University in 1994. A cornerstone in NIAID's global fight against TB, the TBRU contract has been extended through 2007, with the goal of creating a multidisciplinary, international team dedicated to:

- Identifying and improving the understanding of the molecular biology and physiology of *M.tb*;
- Defining the host immune response to mycobacterial infection;
- Developing new epidemiologic tools; and
- Evaluating new or improved drugs, diagnostics, and vaccines preclinically and in phase I–III clinical trials.

Although most of NIAID's TB research is focused on aspects of disease and interventions that are applicable to all TB-affected populations around the world, NIAID is supporting some TB epidemiological studies that are specifically focused on issues relevant to North American Hispanic populations affected by TB. These studies are examining such variables as which

strains of TB are circulating in these populations, risk factors for disease, routes of TB transmission, effectiveness of interventions and treatments, and innovative programs to promote international collaboration among investigators.

## Minority Researchers' Training Programs

Increasing the participation of underrepresented minority investigators in biomedical research is a priority for NIAID and NIH. In addition to supporting NIH-wide programs, NIAID has developed and supported a variety of innovative programs for biomedical research that include minority students from high school through postdoctoral training.

In FY 2005, NIAID extended its longstanding Introduction to Biomedical Research Program. The Richard M. Asofsky Scholars In Research (ASIR) award was created to represent and honor Dr. Asofsky's dedication to bringing underrepresented minorities into the biomedical sciences. The ASIR program provides supplemental funding to NIAID extramural principal investigators for the purpose of supporting underrepresented minority high school and college students in their research laboratories and exposing them to research career opportunities in the areas of allergy, immunology, transplantation, microbiology, and infectious diseases, including AIDS. These NIAID ASIR awards are used to encourage the development of underrepresented minority researchers as outlined in the NIAID *Strategic Plan on Health Disparities*. For more information about the Richard M. Asofsky Scholars In Research award, see: [www.niaid.nih.gov/ibrp/ASOFKSY\\_Research.htm](http://www.niaid.nih.gov/ibrp/ASOFKSY_Research.htm).

Since 1993, NIAID has conducted a symposium designed for recipients of the Research Supplements to Promote Diversity in Health-Related Research, formerly known as Research Supplements for Underrepresented Minorities, to encourage them to continue studies related

to NIAID's biomedical research agenda. In November 2005, NIAID held its seventh Bridging the Career Gap for Underrepresented Minority Scientists symposium. For more information about the symposium, see: [www.niaid.nih.gov/osp/bridging\\_the\\_career\\_gap.htm](http://www.niaid.nih.gov/osp/bridging_the_career_gap.htm).

In an effort to engage scientific discovery and inclusion of minority students in K-12 programs, NIAID held a pilot forum in April 2005 with Washington, D.C., metropolitan area high school science teachers and students entitled Increasing Minority Student Interest in Science, Engineering, and Math: Challenges and Solutions. This was an important outreach effort in NIAID's ongoing commitment to promote an interest in science and research careers among high school students and to increase the numbers of underrepresented minorities involved in scientific research. The students and teachers participated in concurrent workshops that addressed ways to keep minority students interested in science and math and listened to various NIH institute representatives explain their scientific research missions and research training opportunities.

## Training Opportunities in NIAID Laboratories

In February 2005, NIAID's Division of Intramural Research (DIR) Office of Training and Special Emphasis Programs (OTSEP) held its third annual outreach program for underrepresented minorities in the biomedical sciences. This 5-day program on Intramural NIAID Research Opportunities (INRO) included scientific lectures by NIAID researchers, discussions with scientists, and tours of the Research Technologies Branch and the Vaccine Research Center (VRC). Three key features distinguish this new program and will result in more minority students participating in intramural training programs at all levels. Eventually, this programmatic strategy will create a larger pool of potential candidates for

career positions in NIAID. First, the selection of students is based on academic excellence, interest in NIAID research, and desire to participate in NIAID's DIR training programs. Second, current DIR minority trainees are included in all aspects of the program and are invited to give presentations. This allows the visiting students to see first-hand what can be accomplished and to network with the trainees. Third, all participants will be tracked in future years to inform them about NIAID training and professional opportunities and to enlist their participation in OTSEP's outreach activities.

In FY 2005, the OTSEP Underrepresented Minority Programs were fully subscribed for the postbaccalaureate Intramural Research Training Awards (IRTA) traineeships. (See table on page 125 for more information about the career paths of IRTA-sponsored trainees.)

A nationwide marketing strategy proved highly successful in promoting INRO 2005. Historically Black colleges and universities were targeted for outreach. As a result of these activities, the number of qualified applicants nearly doubled to 121. Twenty-six applicants were selected to attend INRO 2005. Twelve INRO 2005 participants were offered training positions in DIR labs; 11 of these students have begun their laboratory traineeships in the following programs: Postdoctoral IRTA, Postbaccalaureate IRTA, Technical IRTA, Summer Research Fellowship Program, and Summer Internship Program.

DIR's Summer Internship Program in the Biomedical Sciences increased this year to 103 students. Using the reduction in the percentage of

White students as an overall measure of diversity, there was a greater diversity this year (50 percent) compared with 2004 (60 percent) and 2003 (67 percent).

## Research Guidelines

In all clinical research, including biomedical and behavioral studies, NIAID complies with the 1993 NIH *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. Congress mandated the establishment of these guidelines in the NIH Revitalization Act of 1993. The guidelines stipulate that women and members of minority groups must be included in all NIH-supported research projects involving human subjects, unless there is a compelling reason that such inclusion would be inappropriate. The guidelines also state that women of childbearing potential should not be routinely excluded from participation in clinical research.

OSPRT staff played a major role in updating the NIH report, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, as required by the Government Accountability Office. OSPRT staff also assisted in the development of the *Outreach Notebook* for extramural principal investigators who conduct or plan to conduct clinical trials with human subjects. For the NIH report, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, see [orwh.od.nih.gov/pubs/Updated2002-2003.pdf](http://orwh.od.nih.gov/pubs/Updated2002-2003.pdf); for the *Outreach Notebook*, see: [orwh.od.nih.gov/inclusion/outreach.pdf](http://orwh.od.nih.gov/inclusion/outreach.pdf).

**Examples of Career Paths of Former IRTA Trainees  
as of September 2005**

<b>GRADUATE STUDIES</b>	
<b>Degree Program</b>	<b>Institution</b>
PPP	Barry University
M.P.H.	George Washington University
	Johns Hopkins University
Ph.D.	California Institute of Technology
	Duke University
	Georgetown University
	Washington University
M.D.	Emory School of Medicine
	George Washington University School of Medicine
	Howard University School of Medicine
	Johns Hopkins University School of Medicine
	Morehouse School of Medicine
	University of California Davis School of Medicine
	University of Maryland School of Medicine
	University of Pittsburgh School of Medicine
	University of Rochester School of Medicine
	University of Virginia School of Medicine
	University of Washington School of Medicine
	Wake Forest School of Medicine
	Wayne State School of Medicine
Wayne State School of Medicine	
M.D./Ph.D.	Albert Einstein School of Medicine
	Cornell/Rockefeller/SloanKettering
	Harvard University
	Mount Sinai School of Medicine
	University of Texas at Austin
	Vanderbilt University
<b>PROFESSIONAL POSITION</b>	
Assistant Professor	Virginia Commonwealth University
	Yale University
Biologist	NIAID, NIH
NIAID Principal Investigator	NIAID, NIH
Program Officer	NIAID, NIH
Public Policy	AIDS ACTION
Science Writer	FASEB
Technician	NIAID, NIH

Key: PPP Postbaccalaureate Premedical Program

## SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections (STIs), also commonly referred to as sexually transmitted diseases (STDs), are a major health problem in the United States. They are also considered to be a critical global health priority because of their relationship to HIV/AIDS and the devastating impact they have on women and infants. It is estimated that more than 65 million people in the United States are living with an incurable STI.<sup>63</sup> According to the Centers for Disease Control and Prevention (CDC), approximately 15.3 million people in the United States become infected with at least one STI annually, with nearly half of these cases occurring in people 15 to 24 years old.<sup>64</sup>

A number of conditions can occur as a consequence of STIs, including infertility, tubal pregnancy, cervical cancer, fetal wastage, low birthweight, congenital or perinatal infection, and other chronic conditions such as neurosyphilis. Moreover, substantial biological evidence demonstrates that a person with other STIs is more likely to both acquire and transmit HIV. Studies indicate that the more prevalent nonulcerative STIs (chlamydia infection, gonorrhea, bacterial vaginosis, and trichomoniasis) and ulcerative diseases (genital herpes, syphilis, and chancroid) increase the risk of HIV transmission by at least two to five times.<sup>65</sup>

NIAID supports research for more effective prevention and treatment approaches to control STIs. These approaches include (1) the development and licensure of vaccines, topical microbicides, and treatments for the microbes that cause STIs; (2) understanding the long-term health impact that sexually transmitted pathogens have in various populations; (3) stimulating basic research on the pathogenesis, immunity, and

structural biology of these pathogens; and (4) developing better and more rapid diagnostics.

To carry out these activities, NIAID supports a broad STI research portfolio ([www.niaid.nih.gov/dmid/stds](http://www.niaid.nih.gov/dmid/stds)) that addresses these diseases through individual investigator-initiated research grants, contracts, and a variety of research programs. Among these programs are the STI and Topical Microbicides Cooperative Research Centers, which bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. This program also supports the development of products to diagnose, treat, and prevent STIs, such as vaccines and topical microbicides. Another program, the STI Clinical Trials Group, conducts clinical trials to test safety and efficacy of interventions aimed at the prevention and control of STIs and to support clinical studies to assess the feasibility and accuracy of diagnostics and screening tests.

NIAID also supports the sequencing of the genomes of sexually transmitted pathogens, including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Haemophilus ducreyi*, *Treponema pallidum*, and *Ureaplasma urealyticum*. This information has provided new insights into the pathogenesis of numerous STIs and is paving the way for development of new diagnostics, drugs, vaccines, and microbicides.

In fiscal year (FY) 2005, NIAID continued to support and encourage the development and evaluation of STI diagnostics and other products through the Small Business Innovation Research mechanism.

Additional STI activities include the following:

- A clinical trial to compare a new oral antibiotic treatment regimen with the one currently recommended for the treatment of primary syphilis. Results from this trial could provide an alternative treatment option.

- A pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes was launched in November 2002. This clinical trial has expanded from 25 to more than 35 sites across the United States and plans to enroll 7,550 women aged 18 to 30. This study, the Herpevac Trial for Women, is being conducted as a public-private partnership with GlaxoSmithKline.
- Over the past two years, the STD Prevention Primate Unit for preclinical evaluation of topical microbicides and vaccines at the University of Washington has evaluated several candidate microbicides for safety (effects on the surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques. Results from this Division of Microbiology and Infectious Diseases-supported testing contract are being coordinated with testing conducted by the Division of Acquired Immunodeficiency Syndrome to facilitate product development and safety and efficacy testing in clinical trials.
- Five Partnerships for Topical Microbicides cooperative agreements were awarded in 2005. This program supports the development of topical microbicides with a proposed dual indication for prevention of HIV/AIDS and an STI or for two STIs. This program requires industry involvement in the partnership.

## Topical Microbicides

NIAID continues to focus a great deal of its STI prevention efforts on the development of virus- and bacteria-killing gels, foams, creams, and films. These substances, known as topical microbicides, are designed to protect against sexual transmission of HIV and other STIs.

Topical microbicides work by killing HIV or other sexually transmitted pathogens or by

creating a barrier that prevents them from entering or binding to cells. Ideally, microbicides would be unnoticeable, fast-acting against HIV and a broad range of other sexually transmitted pathogens, inexpensive, safe for use at least one to two times daily, and easy to store. Microbicides with and without contraceptive properties are needed so that a woman's reproductive decisions do not increase her risk for HIV/STI infection. In addition, microbicides may provide protection to men who have sex with men.

NIAID's research effort for developing topical microbicides includes basic research, preclinical product development, and clinical evaluation. The goal of this comprehensive effort is to support research and development that leads to the identification of safe and effective topical microbicides. NIAID's Strategic Plan for Topical Microbicides provides a detailed, long-range plan for advancing microbicide concepts from the laboratory to clinical trial. For more information about NIAID's Strategic Plan for Topical Microbicides, see [www.niaid.nih.gov/publications/topical\\_microbicide\\_strategic\\_plan.pdf](http://www.niaid.nih.gov/publications/topical_microbicide_strategic_plan.pdf).

A number of NIAID-sponsored programs solicit for topical microbicide research. These include the Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM) and the HIV Microbicide Design and Development Teams (MDDT) program. The IPCP-HTM focuses on iterative preclinical and clinical research for novel microbicide strategies against HIV infection and has two overall goals. The first goal is to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations. The second goal is to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies and then to advance these studies into large safety and efficacy clinical trials within the HIV Prevention Trials Network (HPTN). New awards in FY 2005 focus on development of retrocyclin-based microbicides, attachment, fusion and entry

inhibitor combinations, and the development of innovative methods to measure vaginal immunity and microbicide antiviral activity. The HIV MDDT is a milestone-driven contract program designed to streamline development of microbicide candidates, emphasizing combination products with multiple active agents. Initiation of a phase I safety trial is required within the award period. The first MDDT award was made in FY 2005 to develop a novel dendrimer-based microbicide candidate, SPL7013 (VivaGel™). Additional awards for MDDTs are expected in FY 2006, and an expansion of the program is planned for FY 2007.

NIAID has entered into an agreement with the International Partnership for Microbicides (IPM) to share information and expertise in the effort to develop a vaginal microbicide. This partnership pairs NIAID's expertise in topical microbicide discovery and early product development with IPM's capacity to design optimal microbicide formulations, manufacture clinical lots for testing, and conduct clinical trials. The relationship between NIAID and IPM will accelerate the advancement of candidate microbicides. In FY 2005, the pharmaceutical industry agreed to allow IPM to further the development of three microbicides, supported previously through NIAID's former Microbicide Development Program and the current IPCP-HTM. This agreement was made possible through NIAID's support for and participation in the IPM.

NIAID, in coordination with NIH's Office of AIDS Research, is developing a new microbicide research program to foster the translation of microbicide innovations to preclinical development. This novel milestone-driven program, called the Microbicide Innovation Program (MIP), utilizes the NIH Phased Innovation Award (R21/R33) funding mechanism, which is designed to identify innovative concepts and discoveries relevant to topical microbicides and then, through a milestone-driven, phased program of support,

provide the rationale and evidence needed to determine their merit as they advance along the development path.

NIAID also supports large-scale *in vitro* screening of potential HIV transmission-blocking agents through a contract with Southern Research Institute in Frederick, Maryland. Potential microbicides from the private sector and from academic and government sources are tested in several different assays that mimic the vaginal environment to determine their ability to block HIV transmission from infected T cells to cultures of cells lining the human cervix. In FY 2005, 367 compounds were tested.

Microbicide development also is supported through a NIAID contract with the University of Washington. During the past year, several candidate microbicides were evaluated for safety (effects on the surface tissues and microenvironment of the cervix and vagina) in nonhuman primates. Results from these and other testing efforts will be coordinated to facilitate product development and safety and efficacy testing in clinical trials.

Several promising topical microbicide candidates are in various stages of clinical testing. BufferGel™ is an acid-buffering gel that helps maintain the normal acidic environment of the vagina during coitus to disrupt the transmission of acid-sensitive sexually transmitted pathogens such as HIV. Results from clinical trials conducted by the HPTN in the United States, India, Thailand, Zimbabwe, and Malawi found BufferGel™ to be safe and well-tolerated in uninfected women and men.

The HPTN studies of PRO 2000/5 gel, a synthetic compound that inhibits HIV entry into cells, were completed recently in the United States and Durban and Johannesburg, South Africa. PRO 2000/5 gel was found to be well-tolerated at different concentrations in the two groups tested—sexually active women who

were at low risk of HIV infection and sexually abstinent, asymptomatic, HIV-infected women.

NIAID is currently conducting a phase II/IIb study, called HPTN 035, to further evaluate the safety and effectiveness of these two compounds in preventing HIV infection in women. HPTN 035 is a four-arm, multisite, randomized controlled trial comparing BufferGel™ and 0.5% PRO 2000/5 Gel (P) with a placebo gel

and with no treatment. Approximately 3,220 women will participate in the study. Enrollment is currently being conducted at sites in Philadelphia, Pennsylvania; Lilongwe, Malawi; and Durban and Hlabisa, South Africa. Additional sites in Blantyre, Malawi; Harare and Chitungwiza, Zimbabwe; and possibly Lusaka, Zambia, will join the trial as site preparations are successfully completed.

## TRANSPLANTATION

Transplantation is a powerful mode of treatment for people facing a wide range of congenital and acquired diseases. Today, doctors routinely transplant more than 25 different organs and tissues to treat kidney failure, type 1 diabetes, leukemia, end-stage pulmonary disease, liver disorders, cardiovascular disease, and many other disorders.

Two major impediments to successful transplantation remain, however. The first of these is graft, or transplant, rejection by the body's immune system. Recent research advances provide a much clearer understanding of the immune mechanisms that cause graft rejection. These insights in turn led to better therapies to suppress the immune system, which allows a graft to survive and function. As a result, 1-year graft survival rates have increased for all organs and tissues, and in many cases now exceed 80 percent. But despite this improvement, long-term graft survival rates have not increased nearly as much.

The second barrier to wider use of transplantation is a critical shortage of donor organs and tissues. Nationwide, there are more than 90,000 candidates on waiting lists for organ transplantation: approximately 66,200 for kidneys; 17,500 for livers; 2,500 for pancreas or combined kidney/pancreas transplants; 3,200 for hearts or heart-lung transplants; and more than 3,000 for lung transplants.<sup>66</sup> The demand far outstrips the supply of donor organs in the United States. In 2005, 14,492 individuals were organ donors.<sup>67</sup>

### Immune-Mediated Graft Rejection

To further improve both short- and long-term graft survival, the NIAID Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad portfolio of basic research in transplantation immunology, as well as preclinical evaluation and clinical trials of promising

post-transplant therapies. The major goals of DAIT's transplantation research program are to understand the pathways whereby the immune system recognizes transplanted organs, tissues, and cells; characterize the cellular and molecular components of acute rejection and chronic graft failure; evaluate novel therapies for treating rejection and prolonging graft survival in preclinical models; develop and implement strategies for immune tolerance induction; and conduct clinical trials of new therapies to improve graft survival, while minimizing the toxic side effects of immunosuppressive drugs.

Kidney transplantation, which is the preferred therapy for end-stage renal disease, accounts for 59 percent of all solid organ transplants. The NIAID Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) program was first established in 1994. Its goals are to support multicenter clinical trials of new ways to prevent graft rejection in pediatric kidney transplant patients, evaluate changes in drug regimens intended to limit side effects of immunosuppression, and assess pre-transplant immunotherapies. Ongoing CCTPT clinical trials include an evaluation of the immunosuppressive drug sirolimus for chronic graft failure and a study of the effects of steroid withdrawal in pediatric transplant recipients. CCTPT also conducts immunological studies to determine how these various interventional approaches affect the immune system.

In FY 2004, NIAID collaborated with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute to establish a clinical consortium intended to improve the success of organ transplants. The goals of the consortium are to identify genetic factors in patients that could help doctors predict transplant outcomes and responses to post-transplant therapy; to develop diagnostic tests that enable early detection and ongoing monitoring of immune-related processes; and to

test the safety and effectiveness of new, less toxic immunosuppressive drugs.

NIAID and NIDDK also cooperatively established the Genomics of Transplantation Cooperative Research Program to support interdisciplinary, large-scale genomic studies in clinical transplantation. The goals of the program are to understand the genetic factors that affect immune-mediated graft rejection and to provide a rational basis for the development of more effective strategies for long-term graft survival.

Patients with HIV infection are at high risk for end-stage organ disease. Before the advent of highly active antiretroviral therapy (HAART), people with HIV were generally not considered for transplants because of their poor prognosis. HAART, however, has improved the outlook for HIV-positive patients so that many more HIV-positive patients with end-stage kidney and liver disease are potential transplant candidates. In FY 2003, DAIT and the NIAID Division of AIDS launched a clinical trial of the safety and efficacy of kidney and liver transplantation in patients with HIV. Seventeen participating centers are currently enrolling subjects in this trial.

### Induction of Immune Tolerance

The drug regimens that suppress a patient's immune system usually can prevent graft rejection, but they also can cause serious side effects such as infections and malignancies. Transplant immunologists, therefore, hope to develop treatments that entail lower risks while improving graft survival. One promising alternative is to selectively modify the immune response to establish tolerance to the graft while leaving protective immune responses intact. The Nonhuman Primate Immune Tolerance Cooperative Study Group, cosponsored by NIAID and NIDDK, evaluates novel regimens intended to induce transplant tolerance in animal models. Scientists working in the study group have already demonstrated that kidney and islet transplant patients given tolerogenic regimens

have increased long-term graft acceptance. In FY 2005, the program was expanded to include heart and lung transplantation. To accelerate the research conducted through this program, DAIT also supports breeding colonies of rhesus and cynomolgus monkeys.

With cosponsors NIDDK and the Juvenile Diabetes Research Foundation International, NIAID supports the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. This network clinically evaluates tolerance-inducing therapies for many immune-mediated disorders, including rejection of transplanted organs, tissues, and cells. ITN also conducts studies on the underlying mechanisms of these approaches and develops new ways to measure the induction, maintenance, and loss of immune tolerance in humans. Since its inception, ITN has established a variety of state-of-the-art core facilities, initiated more than 20 clinical protocols, and funded several basic science studies of the mechanisms of induced immune tolerance. More information on ITN is available at [www.immunetolerance.org](http://www.immunetolerance.org).

### Shortage of Donor Organs

The number of organ transplants performed in the United States has increased dramatically, from 12,618 in 1988 to 28,110 in 2005.<sup>68</sup> These numbers would be even higher if more donor organs were available; the waiting list for transplants has quadrupled since 1988. DAIT is addressing this problem by supporting efforts to improve donor registries that identify potential donors and by developing educational initiatives to increase public understanding of organ donation, especially among minority populations.

In FY 2005, NIAID, with cosponsorship from the National Institute of Neurological Diseases and Stroke, awarded five research cooperative agreements under the new program, Human Leukocyte Antigen (HLA) Region Genetics in Immune-Mediated Diseases. The objectives

of this program are to define the association between HLA region genes or genetic markers and immune-mediated diseases, including risk and severity of disease and organ and cell transplantation outcomes. This program is the successor to the International Histocompatibility Working Group (IHWG). More information about the IHWG can be found at <http://www.ihwg.org>.

The use of nonhuman organs, tissues, or cells in human transplantation, called xenotransplantation, is another strategy DAIT is pursuing to increase the supply of transplantable organs and tissues. The potential of xenotransplantation, however, is severely limited by the violent response of the human immune system to nonhuman tissues, and some express concern that infectious agents might

inadvertently be introduced from animal donors into humans. Through xenotransplantation research, DAIT supports projects that might increase understandings of the human immune response to antigens present on cells from nonhuman species and that seek to develop methods for rapid identification and treatment of any infectious diseases that might be caused by organisms present in animal donor tissue.

With each advance in transplantation, a new set of challenges emerges. The most pressing challenges today include improving long-term graft survival, establishing long-term tolerance without immunosuppressive drugs, and reducing lengthy transplant waiting lists. NIAID's basic and clinical research programs in transplantation are committed to meeting these challenges.

## TUBERCULOSIS

NIAID plays a leading role in the NIH tuberculosis (TB) research program. Worldwide TB case rates are increasing primarily because of the ongoing HIV/AIDS epidemic and the development of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* (*M.tb*), the pathogen that causes TB. In response to ongoing public health concerns about the global TB epidemic, NIAID has increased its TB research portfolio steadily over the past decade. The World Health Organization (WHO) estimates that there are approximately 8 million new TB cases annually, with 2 million deaths. This toll makes TB the leading cause of death from a single infectious pathogen worldwide, killing more people than AIDS and malaria combined. Approximately one-third of the world's population is infected with *M.tb*, and 1 in 10 of these individuals likely will develop active TB disease in his or her lifetime. However, persons with a weakened immune system, such as those infected with HIV, have a much higher chance of developing active TB and of dying from this disease. If current trends continue, an estimated 1 billion people will be newly infected by the year 2020, approximately 200 million people will develop active TB, and 35 million will die.<sup>69</sup>

NIAID supports a broad TB research program through its extramural Division of Microbiology and Infectious Diseases (DMID), the Division of AIDS (DAIDS), the Division of Allergy, Immunology and Transplantation (DAIT), and through its intramural program, with particular emphasis on the following areas:

- Basic biology and pathogenesis of *M.tb*, host-pathogen interaction, and host response to TB in animal models and humans. The goal is to understand how the immune system recognizes and responds to bacteria such as *M.tb*, hidden within host cells, and to support research on antigen presentation and stress molecule induction as they relate to activation

of cell-mediated immunity to intracellular pathogens.

- Research into the various stages of TB, including persistent, asymptomatic infection with *M.tb* (latency), reactivation, and progression to active TB. This research strives to identify immune system genes that are activated by mycobacterial infection, especially genes that encode soluble proteins that might be relevant to the development of TB vaccines or therapies, and to elucidate T-lymphocyte recognition of mycobacterial lipid antigens, the role of various cell populations in combating *M.tb* infection, and the function of biological oxidants in protective immune processes.
- Development and testing of vaccines, chemotherapeutics, and diagnostics. This focus includes efforts to promote vaccine-relevant research to identify dominant mycobacterial antigens and novel adjuvants that induce protective cellular immune responses, as well as research on the development of immunologic reagents for early diagnosis and monitoring of disease.
- Development of improved tools for epidemiologic studies.
- Mycobacterial genomics and postgenomic analyses.

Consistent funding support over the past 12 years and the inclusion of applied research into the characterization and prevention of MDR-TB in NIAID's Biodefense and Re-emerging Infectious Diseases research agenda have allowed the Institute to support a number of initiatives and partnerships that have markedly expanded the community of TB researchers. Furthermore, funding initiatives to encourage participation of small companies in the development of new healthcare interventions for TB have resulted in a significant number of new product development projects and approaches, many of which are

expected to be validated within the next several years.

NIAID's extramural TB research program currently supports more than 200 grants and 12 contracts for basic, applied, and clinical TB research. The contracts are designed to fill critical gaps in applying fundamental research findings to the development of new healthcare interventions for TB and to provide tools for the conduct of high quality, ethical human clinical studies and trials. NIAID offers TB researchers contracts to study specific mycobacteria, as well as access to more general scientific contract resources, such as mycobacterial microarrays provided by the Pathogen Functional Genomics Resource Center ([www.niaid.nih.gov/dmid/genomes/pfgrc/guidelines.htm](http://www.niaid.nih.gov/dmid/genomes/pfgrc/guidelines.htm)). For access to genome data, see [www.tigr.org/tdb/mbd/mbinprogress.html](http://www.tigr.org/tdb/mbd/mbinprogress.html). Initiatives to encourage public-private partnerships have resulted in several grant awards focusing on the preclinical development of novel diagnostics, drugs, and vaccine candidates that are expected to enter clinical trials within the next few years.

The development of improved TB vaccines, which are crucial to the long-term control of TB worldwide, is a high priority. In December 2003, NIAID and the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research sponsored a workshop to outline U.S. regulatory requirements for the development and human testing of new TB vaccines ([www.niaid.nih.gov/dmid/meetings/tbvacc.htm](http://www.niaid.nih.gov/dmid/meetings/tbvacc.htm)). Clinical trials of two new TB vaccines that were developed with NIAID support began in 2004. One is a recombinant version of the bacillus Calmette-Guerin vaccine, developed by investigators at the University of California, Los Angeles; the other is an adjuvant-peptide fusion vaccine developed by Corixa Corporation.

Through the DMID-supported Tuberculosis Research Materials and Vaccine Testing contract

with Colorado State University ([www.combs.colostate.edu/microbiology/tb/top.htm](http://www.combs.colostate.edu/microbiology/tb/top.htm)), NIAID provides TB research reagents and preclinical vaccine testing services to qualified investigators throughout the world. By the end of FY 2004, more than 150 new TB vaccine candidates had been tested under this contract. One of these has recently entered human clinical trials and several others are progressing through various stages of preclinical development. Through the Millennium Vaccine contract (Infectious Disease Research Institute, Seattle, Washington), NIAID provides funding to the private sector for the development of improved TB vaccines using existing technology platforms.

In 1994, NIAID established the Tuberculosis Research Unit (TBRU) at Case Western Reserve University ([www.cwru.edu/affil/tbru/index.htm](http://www.cwru.edu/affil/tbru/index.htm)). The grant was recompeted in 1999. The DMID-funded TBRU provides knowledge, tools, and technologies to improve human clinical trials in TB and the capability to conduct clinical studies for the evaluation of new or improved vaccines, therapeutics, and diagnostics. Activities of the TBRU are coordinated with other major organizations involved in TB research, including the Centers for Disease Control and Prevention, U.S. Agency for International Development, FDA, WHO, Global Alliance for TB Drug Development, International Union Against Tuberculosis and Lung Disease, and interested industrial partners.

Development of new drugs and improved and shortened therapeutic regimens to treat and prevent active TB is a longstanding activity within NIAID. The Southern Research Institute (SRI) maintains, under contract with NIAID, the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) to acquire drug candidates for screening against virulent *M.tb*. The SRI also maintains a computerized chemical database of candidate structures, coordinates and distributes compounds for evaluation *in vitro* and in animal models, and reports data

to compound suppliers. TAACF has contacted more than 3,500 chemists throughout the world seeking candidate anti-TB compounds. TAACF has received more than 79,000 compounds from academic and private-sector investigators, principally in the United States and Europe, with growing involvement of scientists in Africa, Asia, Australia, South America, and other regions.<sup>70</sup>

NIAID supports a contract for the Tuberculosis Drug Screening program to provide high-throughput screening services to discover new antimicrobials. The facility supported under this contract provides the capability to test large chemical libraries of compounds for activity against specific biochemical drug targets and against growing microorganisms. In addition to supporting *in vitro* evaluation of compounds from chemical repositories, in FY 2005, DAIDS awarded a research grant to stimulate preclinical research of a new class of therapeutics against TB, in the context of HIV/AIDS.

DAIDS also supports the Animal Model Testing of TB Drugs contract, which provides critical support for investigator-initiated drug discovery, stimulates private sector sponsorship of new drugs, performs comparison and confirmatory studies, and provides information for selection of drug candidates for design of clinical studies. In 2004, DAIDS funded the Pharmacokinetics and Pharmacodynamics Animal Model contract. This contract supports a central facility to identify and evaluate novel compounds for their basic pharmacology and efficacy characteristics, provides critical support for investigator-initiated drug discovery, stimulates private-sector sponsorship of new drugs, performs comparison and confirmatory studies from different sponsors, and provides information for the selection of antimicrobial drug candidates for designing clinical studies. DAIDS continues to support the Tuberculosis Technology Transfer contract, which spurs the translation of anti-tuberculosis discoveries into candidates for development and commercialization ([www.newtbrx.org](http://www.newtbrx.org)).

DAIDS supports clinical trials of new treatment and prevention strategies for tuberculosis in the setting of HIV/AIDS. These investigations are being conducted in countries with a high burden of both TB and HIV. The interactions of these two infections are associated with high mortality, particularly in African nations. DAIDS continues to support research projects designed to develop effective and sustainable clinical management strategies to improve care and foster integration of research on HIV and co-infection pathogens, including tuberculosis. In addition, the NIAID Comprehensive International Program of Research on AIDS supports research studies that address important public health research questions in high-burden countries.

NIAID participates in a public-private partnership, the Global Alliance for Tuberculosis Drug Development ([www.tballiance.org](http://www.tballiance.org)). NIAID, together with WHO, the Rockefeller Foundation, and other international organizations in the TB Alliance, is dedicated to encouraging new therapeutic advances in the absence of industrial sponsorship. Recently, in partnership with the TB Alliance and through the TAACF contract, NIAID contributed to the preclinical safety and efficacy testing in animal models of a novel antibiotic, PA-824. In addition, increased funding through Small Business Innovation Research grants has promoted development and evaluation of new tools for treating and preventing tuberculosis.

DAIT supports a number of individual research projects concerned with basic mechanisms of immunity to *M.tb*. DAIT's research goals and objectives on *M.tb* are to

- Understand how the immune system recognizes and responds to bacteria such as *M.tb*, hidden within host cells, and support research on antigen presentation and stress molecule induction as they relate to activation of cell-mediated immunity to intracellular pathogens;

- Promote vaccine-relevant research to identify dominant mycobacterial antigens and novel adjuvants that induce protective cellular immune responses;
- Promote research on the development of immunologic reagents for early diagnosis and monitoring of disease; and
- Support research on the identification of immune system genes that activate in response to mycobacterial infection, especially genes that encode soluble proteins that might be relevant to the development of TB vaccines or therapies.

Research topics include T-lymphocyte recognition of mycobacterial lipid antigens, the role of various cell populations in combating *M.tb* infection, and the function of biological oxidants in protective immune processes.

DAIT sponsors several projects that support research on TB as well as other infectious diseases such as hepatitis C, malaria, and HIV. Under the Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines program, DAIT supports the HLA Ligand/Motif Online Database, a Web-based, searchable database of human major histocompatibility complex (MHC) molecules and peptide ligands. The database specifies amino acid sequences of peptides derived from viral, bacterial, parasite, and human proteins in association with human class I or class II MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to determine ligand amino acid motifs that will facilitate their research. Support is provided under a NIAID contract to the University of Oklahoma ([hlaligand.ouhsc.edu/index\\_2.html](http://hlaligand.ouhsc.edu/index_2.html))

The NIH Tetramer Facility provides custom synthesis and distribution of soluble MHC-peptide tetramer reagents that can be used to detect antigen-specific T cells. These reagents are provided to approved investigators, who

supply the purified peptides and cover the cost of shipping these peptides and the synthesized tetramer reagents. The Tetramer Facility contract covers the cost of tetramer production and validation/quality control. The Facility serves as both a tetramer production facility and as a research and development facility for the generation of novel tetramer reagents. The contract supports the continuation of this reagent resource, which provides custom-made MHC class I, MHC class I-like, and MHC class II tetramers to the research community. More information about this facility can be found at [www.niaid.nih.gov/reposit/tetramer/index.html](http://www.niaid.nih.gov/reposit/tetramer/index.html). The National Cancer Institute also provides funding for the Tetramer Facility.

Tuberculosis research within NIAID's Division of Intramural Research (DIR) focuses on understanding the molecular pathology of TB with an eye to developing new interventions that will make a substantial difference in disease control. The DIR TB research portfolio forms a spectrum from laboratory to clinic-based studies. DIR scientists collaborate with a wide variety of academic and industrial partners as well as other government agencies to maximize the likelihood that laboratory discoveries will make a difference to clinical practice.

DIR scientists are engaged directly in the identification, design, and synthesis of promising new drug candidates from several chemical series. Nitroimidazoles such as PA-824, which is currently in clinical trials, are a major focus because they have the potential to be effective against both the drug-resistant and drug-sensitive forms of TB. In 2000, DIR researchers working in collaboration with scientists at Pathogenesis Corporation were part of the team that first reported the activity of this series of molecules. DIR scientists have partnered with the Novartis Institute for Tropical Diseases in Singapore, a research institute working on neglected diseases ([www.nitd.novartis.com](http://www.nitd.novartis.com)), to design, synthesize, and test nitroimidazoles other than PA-824

while working to understand the key molecular mechanism of nitroimidazoles. In another structural class, DIR scientists synthesized SQ-109, a more potent, second-generation analog of ethambutol, in partnership with Sequella, Inc ([www.sequella.com](http://www.sequella.com)). This molecule is also advancing towards clinical trials.

DIR TB researchers maintain an active program of genome-scale analyses as applied to drug development. These types of approaches allow both the rapid identification of the target of new antimycobacterial agents and identification of promising new targets for drug design. These techniques are being applied to shorten the course of chemotherapy in an approach known as “chemical genomics.” Partnering with DAIDS and scientists at the National Institute for Pharmaceutical Research and Development in Abuja, Nigeria, DIR is working to transfer knowledge of the application of genomic information and structure-based drug discovery to scientists in TB-endemic sub-Saharan Africa. DIR scientists are also partners with the Korean Ministry of Science and Technology and the Korea Research Institute for Chemical Technology in Taejon, South Korea, in a newly established International Center for TB Drug Development.

In an international partnership that includes scientists from the United Kingdom, United States, Singapore, South Korea, and Mexico, DIR researchers have a leading role in a \$20 million grant awarded jointly by the Bill and Melinda Gates Foundation and the Wellcome Trust as part of the Grand Challenges in Global Health initiative ([www.grandchallengesgh.org](http://www.grandchallengesgh.org)) to develop new therapeutics for the treatment of latent tuberculosis infections. In this effort, DIR works closely with collaborators at the International Tuberculosis Research Center, which is funded by DIR and the Korean Ministry of Health and located at the National Masan Tuberculosis Hospital in South Korea. This grant will make it possible for DIR researchers to perform key experiments to identify vulnerable targets in TB bacilli in latent and chronic TB patients and to be the first to apply modern techniques of molecular imaging to the clinical evaluation of novel agents with anaerobic activity against *M.tb*.

NIAID support for TB research has led to significant advances in the understanding of the basic biology, microbiology, and immunology of TB. These advances will foster the development of new diagnostic tools, vaccine candidates, and therapeutic strategies to prevent and ultimately cure this devastating disease.

## VACCINE RESEARCH AND DEVELOPMENT

Vaccines are perhaps the most powerful tool available to safeguard public health. Since a vaccine to prevent smallpox was invented in the 18<sup>th</sup> century, vaccines have been a safe, effective, and efficient means of preventing infectious diseases and have saved countless lives. In recent years, new technologies and new insights into the human immune system have greatly accelerated progress in vaccine research and have created exciting new opportunities to combat a wide spectrum of infectious diseases.

Because the potential to alleviate human suffering by developing new and more potent vaccines is so great, vaccine research is a top priority for Federal biomedical research. Within the Department of Health and Human Services, NIAID has the central role in vaccine research and development. The Institute's broad research programs on all classes of infectious diseases and the organisms that cause them, together with basic research on the immune system, catalyze its comprehensive efforts to create new and more effective vaccines. Many of these vaccine development activities are carried out in collaboration with scientists in government, industry, and at academic institutions. To set priorities for vaccine development, NIAID weighs the severity of a disease and the health benefits a vaccine might generate and considers the scientific and programmatic opportunities, given the status of scientific knowledge.

The Division of Acquired Immunodeficiency Syndrome (DAIDS) supports the discovery and development of safe and effective vaccines to prevent HIV infection and AIDS worldwide. To reach this goal, DAIDS invests in a comprehensive portfolio of research grants and programs spanning basic vaccine research and preclinical testing of candidate HIV vaccines



*Pneumococcal vaccine trials* in Kenya and Gambia are designed to test a vaccine that prevents diseases caused by *Streptococcus pneumoniae*, a leading cause of death among infants and children in these countries.

through human clinical testing in the United States and internationally.

The Division of Microbiology and Infectious Diseases (DMID) supports a full spectrum of vaccine research to (1) prevent infectious diseases such as tuberculosis (TB), malaria, cytomegalovirus (CMV), group B streptococcus, and chlamydia infection; (2) serve fragile populations such as infants, older people, and immunocompromised people; (3) evaluate novel vaccine approaches such as oral, transcutaneous, and combination vaccines; and (4) improve existing vaccines.

Both DAIDS and DMID support large clinical networks and have vaccine production contracts that provide opportunities to move vaccine concepts into the early stages of clinical evaluation. Infrastructure for regulatory oversight, clinical site monitoring, and data management round out the vaccine development process. In collaboration with the Fogarty International Center, both Divisions support building infrastructure and training for clinical research in the United States and internationally.

The NIAID Dale and Betty Bumpers Vaccine Research Center (VRC) conducts research that facilitates the development of effective vaccines for human disease. The VRC's primary research focus is the development of a preventive vaccine against HIV/AIDS. In addition to its work on HIV, the VRC has expanded the scope of its activities to include research on developing effective vaccines for Ebola and other viral hemorrhagic fevers, for West Nile virus, for SARS-associated coronavirus, for influenza, and improved smallpox vaccines.

The Division of Allergy, Immunology, and Transplantation (DAIT) supports research designed to apply the fundamental principles of immunology to the development of improved vaccines. The Division of Intramural Research (DIR) conducts a wide-ranging vaccine program. Extensive efforts are underway to develop vaccines to prevent diseases with global reach, such as malaria, AIDS, childhood respiratory infections, chlamydia, hepatitis C and E, West Nile, dengue, rabies, and genital herpes.

NIAID has recently developed a Vaccine Immune T-cell and Antibody Laboratory, in Gaithersburg, MD. This new facility will perform validated immune assays in support of phase II/III studies and product licensure and will serve as a Good Laboratory Practices resource for centralized immunogenicity testing across different NIAID-sponsored vaccine projects.

### **Division of Acquired Immunodeficiency Syndrome**

The development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the AIDS epidemic. NIAID is committed to developing a preventive HIV vaccine and toward this end, provides resources and supports basic biomedical research to better understand the relationship between HIV and the immune system, preclinical development of new vaccines, and clinical research and evaluation of novel

vaccines in all phases of clinical trials. NIAID supports exploratory, high-risk, investigator-initiated HIV vaccine research at the earliest stages of concept genesis and evaluation through the Innovation Grants for AIDS Vaccine Research. Other basic vaccine research and design efforts, including testing in animal models, mechanism-of-action studies, and studies of HIV immune correlates, are supported through the HIV Vaccine Research and Design Program. The Integrated Preclinical/Clinical Vaccine Development Program is a multiproject program that supports iterative product development and later stage vaccine optimization.

To help expedite the development of promising HIV/AIDS vaccines, NIAID also has several novel public-private partnerships under a program titled HIV Vaccine Design and Development Teams (HVDDT). These contracts support consortia of scientists with both ideas and product development experience, from industry and/or academia, who have identified promising vaccine concepts ready for accelerated product development. This program is built around milestone-driven contracts to encourage more rapid advancement of these important products into clinical studies. Ten such contracts have been awarded since 2000. All are moving vaccine products rapidly through production and preclinical testing. Each of the original four contractors has developed experimental HIV vaccines that have entered human clinical trials. In 2005, two new HVDDT contracts were awarded to Children's Research Institute (recombinant adeno-associated virus-based vaccines) and Chiron Corporation (alphavirus replicon-based vaccines).

As of November 2005, NIAID had supported 85 HIV vaccine trials (79 phase I, 5 phase II, 1 phase III) with 53 candidate vaccines and 16 adjuvants in over 18,000 volunteers. The majority of the NIAID HIV vaccine clinical trials are conducted through the HIV Vaccine Trials Network (HVTN). Established in 2000 by NIAID, the

HVTN is a comprehensive global network of international scientists and researchers whose mission is to develop and test preventive vaccines against HIV/AIDS. The HVTN conducts all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy. The HVTN's global capacity allows for rapid expansion as vaccine candidates enter the pipeline for testing and development, and for carrying out larger scale studies of suitable vaccines. Spanning four continents, the network includes more than 25 clinical sites in the United States, Africa, Asia, South America, and the Caribbean; an operations and statistical and data management center; and a central laboratory.

The participation of international sites and the involvement of diverse populations through partnerships with host country researchers, governments, and communities are critical components of NIAID's HIV vaccine effort. They allow for studies that examine differences in HIV diversity, genetic background, nutritional status, effects of other infections, and access to health care, all of which could prove crucial to developing an effective vaccine for use around the world. In particular, the international capacity of the network facilitates studies of various HIV subtypes that might affect only a minority of the population, but could be important to the development of a vaccine that would protect people from different circulating strains of the virus.

During the past year, the HVTN initiated or continued several phase I and II HIV vaccine studies. In particular, NIAID, in collaboration with Merck, initiated a Phase IIb "proof-of-concept" trial to evaluate the efficacy of Merck's MRKAd5 HIV-1 gag/pol/nef candidate, a weakened adenovirus-based vaccine designed to prevent infection or delay HIV disease. The trial, which will enroll 1,500 high-risk volunteers in the United States, Caribbean, and South America, is recruiting volunteers.

### **Expanding Global Vaccine Research**

In light of the changing HIV pandemic and the relatively low incidence of HIV infection in industrialized countries, even among higher risk groups, HIV vaccine testing must in large part be carried out internationally. NIAID established the HVTN to build global capacity and infrastructure with a special focus on pursuing an international vaccine research agenda. NIAID is restructuring all of its HIV clinical trials research networks to expand upon and better coordinate its global vaccine research activities, and to increase collaboration, efficiency, and flexibility. The new structure is designed to improve research efforts by encouraging greater integration of vaccine, prevention, and treatment research and by addressing high priority research questions, particularly in resource-limited settings where AIDS is most devastating.

### **Collaboration and Partnerships**

The AIDS Vaccine Research Working Group (AVRWG) assists the NIH in developing a comprehensive research program aimed at expediting the discovery and development of an HIV/AIDS vaccine. The members of the group provide technical assistance to NIH through their assessment of the scientific opportunities, gaps in knowledge, and future directions of HIV vaccine research. As a working group of the NIAID AIDS Research Advisory Committee, the AVRWG makes recommendations to the Directors of NIAID and DAIDS concerning key scientific questions in vaccine development, including new vaccine designs, efforts to understand the mechanisms of protection in animal models, and potential new targets for vaccines.

The Vaccine Developmental Resources Group (VDRG), consisting of NIAID staff and external scientists, was established in FY 2005. This group will assist DAIDS staff in designing and reviewing protocols for the Simian Vaccine Evaluation Units to answer scientific questions

and advance the AIDS vaccine field. The VDRG will also help NIAID assess the need for government support to advance promising candidate vaccines into and through the clinical stages of testing.

A formal collaboration for HIV vaccine research, development, and testing was established in 2003 between the NIAID and the U.S. Army Medical Research and Materiel Command (USAMRMC) through an interagency agreement with the Department of Defense (DoD). This collaboration helps ensure that U.S. government HIV vaccine research is well coordinated, efficient, and comprehensive. The strategic and scientific strengths of the USAMRMC give NIAID greater access to the USAMRMC HIV/AIDS research program focused on vaccine product development. It also allows NIAID access to the extraordinary DoD medical infrastructure and extensive experience in establishing and supporting operations in developing areas. Several vaccine trials have been initiated as part of this collaboration. The most notable is a phase III study, RV144, in Thailand that began in September 2003. RV144 will evaluate an HIV vaccine strategy known as “prime-boost,” which combines two different vaccines, in this case ALVAC-HIV and AIDSVAX B/E. Each vaccine induces a different arm of the immune system. This trial enrolled approximately 16,000 uninfected volunteers by the end of 2005. This collaboration has also led to the initiation of three phase I clinical trials that will evaluate the LFn p24 HIV vaccine, a multiclade HIV-1 DNA plasmid vaccine, in Uganda, and live recombinant modified vaccinia Ankara (MVA)-CMDR (HIV-1 CM235 env/CM240 gag/pol) vaccine in the United States and Thailand. In addition, a vaccine preclinical testing laboratory, utilizing standardized *in vitro* assays and animal models, has been set up at a U.S. Military HIV Research Program (USMHRP) Walter Reed Army Institute of Research site to test vaccines supported by NIAID. This

laboratory will help identify assays and animal models that predict human immunogenicity and help NIAID prioritize further candidates for further development.

NIAID has also led the development of the Partnership for AIDS Vaccine Evaluation (PAVE), which plans and harmonizes clinical trials conducted under the sponsorship of the U.S. Government. The goal of PAVE is to achieve better harmony and increased operational and cost efficiencies in the conduct of HIV vaccine clinical trials with U.S. agencies and their major partners. PAVE is a voluntary consortium that is part of a global effort to share information. It pools intellectual resources and experience to achieve fundamental goals shared by a number of U.S. government agencies that can be achieved more readily through a collaborative process. Members include NIAID’s VRC, DAIDS, and HVTN; the Centers for Disease Control and Prevention (CDC); and DoD’s USMHRP.

Following a proposal by a group of scientists and endorsement by the G-8 and President Bush at the Sea Island Summit in June 2004, the Global HIV Vaccine Enterprise was created to foster collaboration, cooperation, and transparency in the conduct of HIV vaccine research on a global scale. The Enterprise is a voluntary consortium of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS. The overarching purpose is to efficiently bring resources to bear on gaps in HIV vaccine research, while allowing flexibility in how research is carried out. Recently, the Gates Foundation and NIAID sponsored a series of meetings in an effort to develop a strategic plan for the Global HIV Vaccine Enterprise. Their strategic plan was published online in January 2005 in the journal *Public Library of Science Medicine*.<sup>71</sup>

In response to recommendations by the Global HIV Vaccine Enterprise, in 2005, NIAID created a Center for HIV/AIDS Vaccine Immunology

(CHAVI). CHAVI is a virtual center that will link a large group of domestic and international scientists to elucidate the correlates of immune protection against HIV and use that knowledge to design a vaccine to elicit those specific immune responses. CHAVI will support an intensive consortium approach to address key scientific roadblocks to HIV vaccine development and to design, develop, and test novel HIV vaccine candidates, as defined by NIH and as identified by the strategic plan of the Global HIV Vaccine Enterprise. The CHAVI team is expected to be a highly collaborative, cooperative, and interactive team of leading researchers who devote the majority of their time to the application of state-of-the-art immunological tools.

### **Community Outreach**

To help increase awareness and acceptance of clinical HIV vaccine research, NIAID works to build a working relationship with community representatives around the world. Among these efforts, community advisory boards (CABs) are essential components at all NIAID-sponsored vaccine trial sites and within the research network. CABs provide advice and perspective on whether trials are ethical and reasonable based on community concerns.

In addition, in 2001, NIAID launched the National HIV Vaccine Communications Campaign to stimulate and enhance the national dialogue concerning HIV preventive vaccines and to create a supportive environment for future vaccine studies. A steering group represents the diversity of communities affected by the AIDS pandemic and includes nationally recognized leaders in fields such as communications, the media, social marketing, community education and organizing, health care, advocacy, public policy, and HIV prevention. For more information on the HVCC, see page 10.

### **Future Plans**

NIAID will announce awards in response to the Leadership Group and Clinical Trials Units request for applications in 2006 and 2007, respectively. In the interim, NIAID staff will continue to work with the HVTN to expand capabilities and build capacity of existing clinical trial sites. Through the USMHRP-DoD collaboration, NIAID also continues to prepare for multiple vaccine trials at sites in the United States and abroad. NIAID will also continue to work within the Global HIV Vaccine Enterprise to help ensure that the Enterprise scientific plan is implemented and to help update the plan as needed.

### **Division of Microbiology and Infectious Diseases**

Research leading to new and improved vaccines has long been a high priority for DMID. The goal of the DMID Program for the Accelerated Development of Vaccines, established in 1981, is to support research leading to vaccines that will improve health. DMID bases its priorities for vaccine research on the morbidity and mortality associated with each infectious disease, critical evaluation by the Institute of Medicine (IOM) of the National Academy of Sciences, assessment of research gaps and opportunities, and recommendations made by the National Vaccine Advisory Committee and other advisory groups.

DMID designs and implements a comprehensive research program to develop new or improved vaccines. Advances in microbiology, immunology, biotechnology, and other fields are applied to the development of new vaccines and to the improvement of existing vaccines, including

- New vaccines against major diseases caused by respiratory syncytial virus (RSV); malaria; group A and group B streptococci; and other bacterial, parasitic, and fungal infections of both children and adults;

- Improved vaccines against diseases such as influenza virus, viral hepatitis, and TB;
- Vaccines to prevent neonatal infections, such as group B streptococcus, and congenital diseases caused by CMV infection, toxoplasmosis, syphilis, gonorrhea, and chlamydia infections;
- New vaccines to prevent and control emerging diseases, including *Helicobacter pylori*, West Nile virus, severe acute respiratory syndrome (SARS), drug-resistant bacteria such as pneumococcus, and avian influenza; and
- Novel technologies that enhance vaccine effectiveness, such as adjuvants, proteosomes, and plasmid DNA approaches.

Vaccine development is a long process, and is often done in collaboration with researchers in the pharmaceutical industry and academic laboratories. Vaccines are first screened for potential safety and efficacy in preclinical studies, including experiments using cell cultures and animal models. If the candidate vaccine looks promising, it might be evaluated in human clinical studies through the DMID Vaccine Evaluation Network, which includes the Vaccine and Treatment Evaluation Units and other units at universities across the United States. As integral components of NIAID's vaccine research efforts, these vaccine units support carefully planned human clinical trials of novel bacterial, parasitic, and viral vaccines and other biologics in people of all ages and risk categories. DMID also supports research to develop new vaccine approaches that

- Generate long-lasting protective immunity to various infectious agents;
- Favor the development of mucosal immunity or the production of a specific antibody;

- Increase the immunogenicity of candidate vaccines or favor the expression of a cell-mediated cytotoxic immune response; and
- Simplify immunization regimens to reduce the number of immunizations required for protection.

DMID is internationally recognized as an effective participant in vaccine research and development issues with both U.S. and global impact. In the United States, DMID collaborates with other Federal agencies, including the CDC and the Food and Drug Administration (FDA), on issues of vaccine research, vaccine safety, and national immunization strategies; this collaboration is coordinated through the National Vaccine Program Office (NVPO). Internationally, DMID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization and the Multilateral Initiative on Malaria. DMID, together with the World Health Organization, U.S. Agency for International Development (USAID), Children's Vaccine Program at the Program for Appropriate Technology in Health, Wyeth Vaccines, and the London-based Medical Research Council, supported a randomized, controlled phase III efficacy trial in The Gambia, West Africa, to evaluate a pneumococcal conjugate vaccine manufactured by Wyeth containing nine separate antigens; the trial was designed to determine the impact of the vaccine on childhood pneumonia, which is a major cause of mortality in children under 5 years of age in this region. The results of this study indicated that a large proportion of pneumococcal infections in children in developing countries can be prevented by pneumococcal vaccination. For more information about this trial, see [www.niaid.nih.gov/dmid/gambia](http://www.niaid.nih.gov/dmid/gambia).

Safety is evaluated in every vaccine clinical trial sponsored by DMID; all participants are monitored closely for any adverse effects of the

vaccinations they receive. Specific safety issues such as the use of novel cell substrates for vaccine manufacture and the evaluation of combination vaccines are explored through scientific consultation with other Federal agencies and in coordination with NVPO.

DMID also funds research to better understand safety of the vaccine preservative thimerosal. Since the 1930s, thimerosal has been added to some vaccines and other products because it kills bacteria and prevents bacterial contamination, particularly in multidose containers. When thimerosal is degraded or metabolized, one product is ethyl mercury, an organic derivative of mercury. Little is known about the effects of thimerosal exposure on humans and how it compares to methyl mercury exposure, another organic mercury derivative. To learn more, DMID has initiated several research activities aimed at better understanding what happens to thimerosal once it is introduced into the body and how this compares to current knowledge of the pathway that metabolizes methyl mercury. DMID supported initial studies at the University of Rochester and continues followup studies in Argentina to measure mercury in blood and other samples from infants who received routine immunizations with thimerosal-containing vaccines. In addition, DMID and the National Institute of Environmental Health Sciences cosponsored a study in infant macaques to examine the pharmacokinetics and tissue distribution of thimerosal (given by injection) or methyl mercury (given orally). This study compared levels of mercury in blood and brain after exposure to either thimerosal or methyl mercury. Study results were published online in *Environmental Health Perspectives* in April 2005.<sup>72</sup>

To address concerns regarding specific vaccine safety issues, NIAID and CDC requested that the IOM establish an independent expert committee to review hypotheses regarding possible relationships between specific vaccines and adverse events. In response, IOM created

the Immunization Safety Review Committee in September 2000. This committee reviewed the state of knowledge about various specific immunization safety concerns and communicated its findings to healthcare providers and the public. From 2001 to 2004, the committee met to review several important vaccine safety issues, including measles-mumps-rubella vaccine and autism, thimerosal-containing vaccines and neurodevelopmental disorders, multiple immunizations and immune dysfunction, hepatitis vaccine and neurological disorders, SV40 contamination of polio vaccine and cancer, the potential role of vaccinations in sudden unexpected death in infancy, influenza vaccine and possible neurologic complications, and vaccines and autism. Within several months of each meeting, the committee published reports of its findings and made recommendations about any additional actions that might be indicated.

DMID will continue to apply the latest advances in the fields of immunology, microbiology, and biotechnology to the development of new or improved vaccines against infectious diseases. Some recent applications of new technologies to vaccines include:

- Use of recombinant DNA technology for the production of defined immunogens—antigens that provoke an immune response—as well as the preparation of plasmid DNA vaccines;
- Development and use of various immunomodulators to augment the immune response to poorly immunogenic candidate vaccines;
- Development of novel vaccine delivery systems to promote long-lasting immunity or to generate an immune response in specific host tissues; and
- Research on novel approaches to the development of multicomponent vaccines and simpler vaccination regimens to reduce

healthcare costs and the number of visits to healthcare facilities.

## Division of Allergy, Immunology, and Transplantation

DAIT supports research on immunologic mechanisms and novel technologies applicable to vaccine design and development. The Division funds vaccine-related research projects on innate and adaptive immunity that aim to increase our ability to manipulate immune responses through better understanding of the underlying molecular, cellular, and systemic aspects of natural host defenses and antigen-specific immunity. Basic research topics that sustain vaccine development include innate immune receptors for pathogen molecules, antigen processing and presentation, the development of antibody and cellular immune responses, and the elaboration of immunologic memory. Topics more immediate to vaccine applications include the development of new adjuvants to enhance immunity, the design of approaches that can induce protection in mucosal tissues, and the discovery of new ways to more effectively deliver immunizing agents. Other research that lays the groundwork for improved vaccines includes discovery of new pathogen epitopes—molecular structures of bacteria and viruses that stimulate immunity—and analyses of how variability in the human genome affects immune responses.

DAIT's Human Immunology Centers of Excellence Program supports many mechanistic studies that will contribute to basic understandings of human immunity and responses to vaccines.

In FY 2002, the Hyperaccelerated Award/Mechanisms in Immunomodulation Trials research program was expanded to support in-depth study of immunologic mechanisms during clinical trials of vaccines, including analyses of the underlying mechanisms of protective immunity, specificity and kinetics of

immune responses, and immunologic memory. Studies proposed under this program must make use of clinical samples from a clinical trial supported by other funding. For example, NIAID recently funded research to analyze the cell-mediated immune responses of participants in a smallpox vaccine clinical trial.

DAIT supports the HLA (human leukocyte antigen) Ligand/Motif Online Database, a Web-based, searchable database of human major histocompatibility complex (MHC) molecules and the protein fragments that bind them. The database specifies the amino acid sequences of peptides derived from viral, bacterial, parasite, and human proteins in association with human MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to identify specific amino acid sequences that bind MHC molecules. The database is funded through a contract with the University of Oklahoma; further information is available at <http://hlaligand.ouhsc.edu>.

The Modeling Immunity for Biodefense Program was established to support development of innovative and functional mathematical models of immunity to infection, vaccines, or other therapeutic interventions with a focus on NIAID Category A, B, and C priority pathogens.

Contracts awarded under the Population Genetics and Analysis Program focus on identification of the genetic variation in human immune response genes that contribute to variations in immune responses to vaccination or infection.

The Immune Epitope Database and Analysis Program was established to develop and maintain an integrated, Web-based searchable database of antibody binding sites (B cell epitopes) and antigenic MHC-binding peptides (T cell epitopes) for a wide variety of infectious agents and immune-mediated diseases, with emphasis on Category A, B, and C bioterrorism agents, as well as emerging/re-emerging infectious diseases.

The Immune Function in Special Populations program is aimed at identifying biological mechanisms responsible for immunosuppression. It also develops protocols to enhance vaccinations and immunotherapies in immunocompromised individuals. These special populations include neonates, infants, the elderly, pregnant women, and individuals with primary immunodeficiency diseases or drug-induced immunosuppression resulting from cancer or post-transplant therapy.

Grants funded under the Cooperative Centers for Translational Research on Human Immunology and Biodefense program will facilitate the translation of research results from animal models such as the mouse into studies in humans. This program will develop new technologies to study human immune responses and regulation and will fund research on human immune responses to NIAID Biodefense Category A, B, and C priority pathogens.

Contracts awarded under the Innate Immune Receptors and Adjuvant Discovery program support research on new adjuvants—additives that help stimulate human immune responses—from initial evaluation through preclinical testing. The adjuvant products developed under this program might be used both as vaccine adjuvants—to elicit T and B cell responses when co-administered with an immunogen—and as stand-alone immunomodulators that can stimulate short-term protective responses against many different infectious agents.

The Large-Scale Antibody and T Cell Epitope Discovery Program supports the rapid identification and verification of the specific molecular structures on pathogens, called epitopes, that antibodies or T cells recognize during the immune response. A related effort will establish a comprehensive, centralized database to provide a Web-based, searchable source of information on pathogen epitopes for researchers. Included in the database is an analysis resource

to facilitate data analysis and prediction of novel pathogen epitopes.

The NIAID Tetramer Facility produces MHC/peptide reagents that help detect T cells with specific response characteristics; this program, which is also funded in part by the National Cancer Institute, has so far provided more than 2,300 tetramers to investigators worldwide. Reagents are provided for the study of T cell responses relevant to vaccine research and development for many diseases including intracellular bacterial, viral, and parasite infections and autoimmune diseases. Information on the NIAID Tetramer Facility can be found at [www.niaid.nih.gov/reposit/tetramer/index.html](http://www.niaid.nih.gov/reposit/tetramer/index.html).

## Division of Intramural Research

The Division of Intramural Research conducts basic and applied research to develop vaccines against many infectious diseases, including pandemic influenza, malaria, pediatric respiratory diseases, SARS, hepatitis, rotaviral diarrhea, dengue, St. Louis encephalitis, and West Nile fever. Vaccine candidates for many of these diseases are currently in clinical trials. This work often involves collaborative research and development efforts that span years—or decades—before coming to fruition. For example, FluMist<sup>®</sup>, the live, attenuated, intranasal influenza vaccine, is the result of more than 20 years of collaborative research involving Dr. John Maassab of the University of Michigan School of Public Health and DIR scientists, with support from NIAID.

Today, scientists in the DIR Laboratory of Infectious Diseases are among the world's foremost experts in the development of live, attenuated vaccines (LAV) such as FluMist<sup>®</sup>. LAVs are made by using specialized techniques to attenuate or weaken a virus so that it can be safely administered in a form that closely mimics natural infection. This process stimulates both local and systemic immunity, resulting in a robust immune response. At its best, a live, attenuated

vaccine gives a broader and more potent immune response than a killed vaccine formulation. LAV vaccines for measles, mumps, and rubella stimulate life-long immunity and have a long history of safety and effectiveness. However, like other types of vaccines, live vaccines have advantages and disadvantages that affect their suitability for particular applications.

For example, RSV is the most important cause of serious pediatric respiratory disease worldwide, resulting in the hospitalization of more than 100,000 infants and young children each year in the United States alone. In the 1960s, an experimental RSV vaccine made from killed virus caused a phenomenon called immune-mediated disease enhancement, which resulted in severe disease among some vaccine recipients upon natural exposure to the virus. Since then, other approaches have been pursued by RSV vaccine researchers in the DIR and elsewhere. DIR scientists and their collaborators have worked many years to develop a safe RSV vaccine, and recently developed and evaluated a recombinant LAV candidate for RSV. In a clinical trial with 1- to 2-month old infants, the vaccine was well-tolerated and stimulated an immune response that was protective against a second vaccine dose. Additional RSV vaccine candidates are in line to be evaluated clinically, and it is likely that one or more superior candidates will be identified.<sup>73</sup>

In 2005, efforts to develop avian influenza vaccines took on greater urgency as the deadly H5N1 avian influenza strain continued to circulate in Asia and was found in several Eastern European countries. NIAID is pursuing multiple approaches to speed the manufacture of pandemic flu vaccines, and development and evaluation of both killed and live virus vaccines is underway.

Again drawing upon their LAV expertise, DIR researchers initiated work under a cooperative research and development agreement (CRADA) with MedImmune, Inc., to develop a panel of live, attenuated avian influenza viruses with

pandemic potential. Under the CRADA, DIR and MedImmune scientists will produce and test multiple vaccines against potential pandemic flu strains, starting with the H5N1 strain. In addition, DIR scientists are continuing work begun several years ago following the emergence of an H9N2 avian flu strain in Hong Kong and China that caused several human infections. A live virus vaccine developed by DIR and CDC scientists against this H9N2 avian virus has completed phase I clinical testing for safety and efficacy.

Live-attenuated vaccines for pandemic influenza may be particularly useful because they could very rapidly induce immunity in persons with no previous exposure to the virus and might be effective with a relatively small dose. An LAV could also stimulate effective immunity to a circulating pandemic virus that differs significantly from the vaccine strain, a real possibility given both the biology of influenza viruses and the lengthy flu vaccine production process. In addition, an intranasal LAV pandemic flu vaccine could be easily administered by nonmedical personnel or given as a booster to a killed vaccine.

To mitigate concerns about the possibility of a pandemic vaccine virus reassorting with a seasonal influenza virus, deployment of an intranasal LAV pandemic flu vaccine would likely have to await clear evidence that human-to-human transmission of an avian virus had reached the pandemic stage. However, pursuing multiple strategies to develop pandemic influenza vaccines increases the odds that effective weapons will be available if they are needed.

While pandemic influenza vaccines are receiving increasing attention and resources, other important DIR vaccine programs continue in earnest, particularly the malaria vaccine programs underway in DIR's Malaria Vaccine Development Branch (MVDB). The MVDB maintains collaborations with researchers in the

United States and throughout the world; it also works closely with a variety of funding agencies, including the USAID and the Malaria Vaccine Initiative sponsored by the Bill and Melinda Gates Foundation. The MVDB has several malaria vaccine candidates in clinical trials in the United States and in malaria-endemic countries, and several more vaccine candidates in preclinical testing or under development in the laboratory. Additional information can be found in the malaria section on page 111.

### Vaccine Research Center

The NIAID Vaccine Research Center is dedicated to translating basic science knowledge into clinical vaccine products. This requires the ability to do basic research, construct new vaccine products, perform preclinical research, and evaluate candidate vaccines in phase I human studies. To conduct human clinical trials, the VRC has established the infrastructure to produce vaccine products using good manufacturing practices, and to manage regulatory issues related to human trials. This includes a dedicated clinical trials staff for volunteer recruitment and clinical evaluation of approximately 300 healthy adult volunteers per year.

The VRC's prime-boost vaccine candidate, which uses a multiclade multigene DNA plasmid vector prime, adenoviral vector (ADV) boost strategy, has progressed through phase I clinical trials. The VRC has been given permission by the U.S. FDA to proceed with a phase II trial. The two vaccines (6-plasmid DNA and 4-vector ADV) developed by the VRC incorporate HIV genetic material from clades A, B, and C, which cause about 90 percent of all HIV infections around the world. These are the first multigene, multiclade HIV vaccines to reach clinical phase II, marking an important milestone in the search for a single vaccine strategy that targets U.S. subtypes of HIV as well as clades causing the global epidemic. In phase I studies of the separate components,

the vaccines were shown to be well tolerated and elicited cellular and humoral responses. A recently launched trio of trials of this prime-boost strategy, sponsored by DAIDS and to be conducted by three international networks, the HVTN, the International AIDS Vaccine Initiative, and USMHRP, will test the safety and immunogenicity of the prime-boost strategy in the Americas, Southern Africa, and Eastern Africa.

The VRC also develops vaccines for biodefense. For example:

- Investigators at the VRC, with scientific collaborators at the U.S. Army Medical Research Institute for Infectious Diseases, and the CDC, have developed a potentially effective vaccine strategy for Ebola virus infection in nonhuman primates. In November 2003, the VRC initiated the first human clinical trial of a DNA vaccine designed to prevent Ebola infection. The vaccine was well tolerated at all dose levels, and there is evidence of both humoral and cellular immune responses at all doses. Final data analysis is currently in progress.
- The VRC plans to evaluate a fast-acting, recombinant adenoviral vector (rAd) Ebola vaccine. Such a vaccine would be especially useful in an acute outbreak setting. If this vaccine proves to be effective in humans, it could one day be used to quickly contain Ebola outbreaks with the same ring vaccination strategy used in the past against smallpox. This product is currently in the preclinical testing phase, and a phase I study is projected to begin midyear 2006.
- Preclinical development work is evaluating another Ebola preventive regimen that could include either a rAd Ebola vaccine alone, or a DNA prime-rAd Ebola vaccine boost approach.

- The VRC is currently testing MVA as an attenuated poxvirus with the potential to protect against vaccinia (the virus used to vaccinate against smallpox) or variola (the virus that causes smallpox). The vaccine was provided by Therion Biologics Corporation as part of a collaboration with the VRC. Two phase I clinical trials testing MVA as a component of a safer smallpox vaccine in both vaccinia-naïve and vaccinia-immune populations were recently completed.

The VRC is developing vaccines for naturally emerging infections such as West Nile virus and SARS. For West Nile, in April 2005, following preclinical safety studies and viral challenge studies, the VRC initiated a phase I clinical trial to evaluate safety, tolerability, and immune responses of a candidate recombinant DNA vaccine in human volunteers. In response to the recent global outbreak of SARS, VRC investigators began work immediately on the development of a potential vaccine. A CRADA and contract were established with GenVec, Inc., to produce preclinical and clinical grade adenoviral vectors that express several SARS proteins. The NIAID Vaccine Research Center

plans to evaluate the immunogenicity of these vectors preclinically, and will continue to develop and test adenovector-based vaccine candidates against SARS that are suitable for rapid advancement toward clinical trials. In addition, the VRC has contracted with Vical, Inc., to manufacture a SARS DNA-based vaccine encoding the spike (S) glycoprotein of the SARS coronavirus. Recent studies have demonstrated that this vaccine induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model. A phase I trial of this recombinant DNA vaccine developed at the VRC was initiated in mid-December, 2004.

Finally, VRC is constructing a contractor-leased and -operated Vaccine Pilot Plant (VPP), which will manage production of multiple vaccine candidates originating from VRC. To achieve this high priority objective, VPP will coordinate with the Vaccine Production Laboratory located at the NIH campus in Bethesda, Maryland, to transfer new vaccine technology for pilot-scale production of vaccine material for use in clinical trials. The VPP will be a self-contained facility of 126,900 square feet with the capacity to produce four to eight clinical lots of vaccine annually.

## NIAID-SUPPORTED REPOSITORIES

NIAID's intramural and extramural researchers have developed a substantial array of resources and reagents that are used by scientists worldwide for basic research, applied research to develop therapeutics and vaccines, and commercialization. These resources include peptides, cell lines, monoclonal antibodies, viral vectors, and animal models.

### Division of Acquired Immunodeficiency Syndrome (DAIDS)

#### *NIH AIDS Research and Reference Reagent Program*

The NIH AIDS Research and Reference Reagent Program acquires and distributes state-of-the-art reagents for AIDS-related research and makes these reagents available to qualified investigators throughout the world. It has grown significantly during the past 18 years and now has more than 6,500 reagents for public distribution. The AIDS Research and Reference Reagent Program also encourages and facilitates technology transfer through workshops, publication of methods, and provision of standardized panels and protocols; facilitates commercial development of reagents; and participates as an AIDS Collaborating Center of the World Health Organization (WHO).

The reagent program has immortalized and expanded white blood cells from more than 9,000 specimens from DAIDS-supported cohort studies of HIV-infected people, including the Multicenter AIDS Cohort Study, Women's Interagency HIV Study, and Women and Infants Transmission Study. These preserved cells will provide a source of DNA for future studies of genetic factors in HIV disease. By making these specimens available to the scientific community, DAIDS fosters collaboration among scientific investigators to promote further progress in the

detection, treatment, and prevention of HIV disease. More than 2,800 scientific publications have resulted from the use of reagents supplied by the NIH AIDS Reagent Program. To date, scientists from the United States and 66 foreign countries have been registered to receive reagents. In 2005 alone, more than 20,000 reagents were distributed.

In 2003, the reagent program contract jump-started the acquisition and distribution of urgently needed quality-controlled reagents for research on biodefense and emerging infectious disease agents such as anthrax and severe acute respiratory syndrome. In 2005, the contract was competitively awarded to the incumbent contractor, Fisher BioServices, Inc.

Additional information is available at [www.aidsreagent.org](http://www.aidsreagent.org).

#### *Vaccine Reagent Resource*

Through the Vaccine Reagent Resource, DAIDS provides resources for the production or procurement of reagents essential for vaccine studies conducted by the HIV Vaccine Trials Network and the Simian Vaccine Evaluation Units, as well as other priority vaccine studies. These resources also provide for the testing of reagents to ensure quality. Additional information is available at [www.niaid.nih.gov/daids/vaccine/reagentres.htm](http://www.niaid.nih.gov/daids/vaccine/reagentres.htm).

#### *Human HIV Specimens*

Research on HIV transmission and disease progression patterns greatly benefits from a centralized system for receiving, cataloging, storing, and distributing samples collected from various well-characterized cohorts of HIV-infected individuals. Through a specimen repository contract with BBI Biotech, NIAID provides state-of-the-art storage and computerized inventory management of specimens from domestic and international HIV epidemiology studies, HIV therapeutic and vaccine trials, and other prevention

research studies through its central repositories. In addition, the National Disease Research Interchange (NDRI), supported through the NIH's National Center for Research Resources cooperative agreement, collects, distributes, and maintains a repository of a wide range of tissues from HIV-positive donors for distribution to qualified biomedical research scientists. Now in its 14<sup>th</sup> year of funding, over 30 NIH HIV/AIDS investigators have registered with NDRI to receive tissues, and over 600 tissues from HIV-positive donors have been shipped. Researchers can register for tissues and see the catalog of services at [www.ndriresource.org](http://www.ndriresource.org).

## **Division of Allergy, Immunology, and Transplantation (DAIT)**

### **Multiple Autoimmune Disease Genetics Consortium (MADGC)**

Different autoimmune diseases are often found within a single family, suggesting common genetic contributions to the diseases. MADGC is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This repository provides well-characterized materials for use in research aimed at identifying the genes involved in autoimmune diseases in 363 families. MADGC began enrolling families in May 2000. Additional information is available at [www.madgc.org](http://www.madgc.org).

### **Primary Immunodeficiency Diseases Registry (PIDR)**

PIDR was established by NIAID to maintain clinical information on patients in the United States affected by primary immunodeficiency diseases. For each disease, the registry collects information on the natural course of the disease, including early and late complications, effects of therapy, and causes of death. The diseases included in the registry are chronic granulomatous disease, hyper-IgM syndrome, severe combined immunodeficiency disease,

X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency, leukocyte-adhesion deficiency, and DiGeorge syndrome. Researchers can apply to the registry to request contact information for physicians who are caring for primary immunodeficiency disease patients. In 2003, a repository was established. The repository contains cell lines from patients with primary immunodeficiency diseases. Researchers can apply to the repository for access to this material. For PIDR-related repository information, see [www.usidnet.org/index.aspx?sid=3](http://www.usidnet.org/index.aspx?sid=3).

### **National MHC Tetramer Core Facility**

In FY 1998, NIAID established a contract facility to provide researchers with peptide-major histocompatibility complex (MHC) tetrameric molecules for analyzing antigen-specific T cell responses. Because T cells are central to virtually all immune responses, this technology is applicable to studies in many areas including basic immune mechanisms, infectious diseases, vaccination, autoimmunity, transplant rejection, and tumor therapy. By centralizing the production of these tetramers, individual defined peptide-MHC molecules can be produced economically and can be made available to investigators at greatly reduced expense. The MHC tetramer core facility is located at Emory University in Atlanta, Georgia, under the direction of John Altman, Ph.D. For more information about the MHC Tetramer Core Facility see [www.niaid.nih.gov/posit/tetramer/overview.html](http://www.niaid.nih.gov/posit/tetramer/overview.html).

## **Division of Intramural Research (DIR)**

### **Transgenic and Gene-Targeted Mice Repository**

DIR, in collaboration with DAIT, supports facilities for the acquisition, breeding, and distribution of transgenic and gene-targeted (knockout) mice, which are mice that are genetically engineered to serve as animal models

for human disease research. The repository provides these mice to both intramural and extramural investigators through the NIAID/Taconic exchange programs for use in research and for development of clinical therapies in various infectious and immunologic diseases.

## Division of Microbiology and Infectious Diseases (DMID)

### Global Health

#### Malaria Research and Reference Reagent Repository

The malaria repository was established to acquire, produce, and distribute malaria research reagents, reference materials, and other information to qualified investigators throughout the world. Major goals of the program are the quality control of reagents, standardization of protocols, and exploration of new technologies. International workshops and training sessions will be organized to stimulate and support both laboratory-based and field-based research. The long-term goal of the repository program is to promote technology transfer as well as to facilitate research leading to commercial development of reagents for malaria diagnostics, prevention, and treatment. NIAID established the repository in support of the Multilateral Initiative on Malaria, a research capacity-strengthening program in partnership with other national and international organizations. Additional information is available at [www.malaria.mr4.org](http://www.malaria.mr4.org).

#### Tuberculosis Research Materials and Vaccine Testing

*Mycobacterium tuberculosis* (*M.tb*), the organism responsible for tuberculosis (TB), is difficult and time-consuming to grow and, because it is transmitted via aerosols, should be studied only in appropriate biohazard facilities. DMID funds a repository to provide *M.tb*-derived materials to qualified TB investigators in basic and clinical research worldwide, allowing work to begin quickly and eliminating the need for

these investigators to have their own biohazard facilities. DMID also supports the screening of potential anti-TB vaccine candidates, which are provided by individual researchers, in established small-animal, low-dose, aerosol-challenge models. Additional information is available at [www.cvmb.colostate.edu/microbiology/tb/top.htm](http://www.cvmb.colostate.edu/microbiology/tb/top.htm).

#### Leprosy Research Support and Armadillo Colony

Despite the availability of multidrug regimens to cure leprosy, leprosy has remained a problem worldwide. A major obstacle in leprosy research is the fact that *Mycobacterium leprae* (*M. leprae*), the organism responsible for leprosy, cannot be cultured in laboratory media and therefore must be propagated in animals. To help alleviate this problem, DMID supports the maintenance of an armadillo colony, one of the best animal model systems of *M. leprae* infection and disease. DMID also funds a repository of viable *M. leprae* and purified, defined reagents derived from *M. leprae*, which are available to researchers worldwide. Additional information is available at [www.cvmb.colostate.edu/mip/leprosy/index.html](http://www.cvmb.colostate.edu/mip/leprosy/index.html).

#### Shiga Toxin-Producing Escherichia Coli (STEC) Center

The STEC Center is designed to facilitate research on the Shiga-toxin producing *Escherichia coli* (*E. coli*) by providing a standard reference collection of well-characterized strains and central online accessible databases. The center was established to act as a repository for deposition of STEC from new outbreaks and environments as they are identified, establish and distribute sets of STEC reference strains for use by investigators, conduct rapid characterization of STEC based on genetic markers of clonal identity and virulence genes (sequencing of flagellin and toxin genes will be performed in order to subtype strains), and make typing data of STEC available to the scientific community by developing and maintaining online databases. For more

information, visit <http://www.shigatox.net/cgi-bin/stec/index>.

### Schistosomiasis Resource Center and Filariasis Research Reagent Repository Center

For more than 30 years, NIAID contracts have supported two helminth resources that serve the research community. The Schistosome Resource Center ([www.schisto-resource.org](http://www.schisto-resource.org)) is maintained by the Biomedical Research Institute (Dr. Fred Lewis, Principal Investigator), and the Filariasis Research Reagent Repository Center ([www.filariasiscenter.org](http://www.filariasiscenter.org)) is maintained by the University of Georgia (Dr. John McCall, Principal Investigator). Investigators worldwide can obtain schistosome or filaria life stages for research or teaching purposes. Selected materials, including molecular and genomic reagents, are made available to biochemists, immunologists, vector biologists, and others who cannot reasonably maintain their own life cycles due to lack of space, time, funding, or requisite expertise. Investigators can obtain parasites, vectors, and mammalian hosts free of charge, excluding shipping costs. In addition to fostering schistosomiasis and filarial research, these two NIAID resources serve as valuable backup facilities for investigators.

### Pneumococcal Reference Laboratory

This laboratory provides reference and resource services and expertise to facilitate the evaluation of improved pneumococcal vaccines and other bacterial respiratory pathogens. A major objective is to establish a consensus assay and to improve procedures for measuring antibody activity to pneumococci. The laboratory also provides radio-labeled polyribosylribose phosphate (PRP) and/or suitably derivatized PRP and purified PRP to laboratories for the performance of *Haemophilus influenzae* type B assays and for calibration of immunodiagnostic assays.

### Viral Infections

#### Repository for Biological Reagents and Reference Standards

This repository stores and distributes serological and microbiological reagents for use as reference standards and for research in infectious and immunologic diseases. As a World Health Organization (WHO) Collaborating Center for Antiviral Drugs and Interferon, this NIAID repository is responsible for the storage and worldwide distribution of WHO international interferon standards and reference reagents.

#### In Vitro Antiviral Screening Program

NIAID maintains a screening program to provide *in vitro* screens for evaluation of potential antiviral agents for inhibitory activity against herpesviruses (herpes simplex viruses 1 and 2), varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, (human herpesvirus 6 and 8), orthopoxviruses (vaccinia and cowpox), respiratory viruses (influenza A, influenza B, parainfluenza, respiratory syncytial virus, measles, rhinoviruses, adenoviruses, and severe acute respiratory syndrome coronavirus), viral hemorrhagic fevers and encephalitic viruses (Venezuelan equine encephalitis, Pichinde, Punta Toro, yellow fever, West Nile virus, and dengue fever), hepatitis B and C, BK virus, and papillomaviruses. These *in vitro* screens provide selective indexes of potential compounds, thus providing early information to guide selection and prioritization. Active compounds can then be evaluated against several virus strains and for assessment of pharmacologic properties.

#### World Reference Center for Emerging Viruses and Arboviruses

NIAID maintains the World Reference Center for Emerging Viruses and Arboviruses at the University of Texas Medical Branch at Galveston. The Center has reference virus sera and seed lots of various virus strains, which can be distributed to qualified researchers and facilities.

Although focused primarily on arthropod-borne and rodent-borne viruses, other viral reagents are also available. This international program involves characterizing viruses transmitted to people and animals by mosquitoes and other arthropod vectors or animal hosts and researching the epidemiology of arboviruses and emerging viruses in the United States and in other countries. Center activities include (1) virus identification and characterization; (2) investigation and diagnosis of disease outbreaks; (3) preparation and distribution of certified virus stocks and reagents to qualified investigators/facilities; (4) development of new animal models of arboviral and other emerging diseases and studies of arboviral pathogenesis; (5) training of professional and technical personnel from any region of the world in arbovirus techniques; and (6) dissemination of information on arbovirus taxonomy, diagnostic techniques, and disease outbreaks. Because of the center's extensive virus reference collection, unique diagnostic capabilities, and contact with virologists and public health laboratories throughout the world, it plays an important role in the global surveillance network for emerging viral diseases.

## Biodefense and Emerging Infectious Diseases

### The Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA)

NARSA is a multidisciplinary international network of basic scientists, clinical microbiologists, and clinical investigators that focuses on *Staphylococcus aureus* (*S. aureus*) and other staphylococcal species that exhibit antimicrobial resistance. NARSA is responsible for tracking and procuring staphylococcal isolates (including *S. aureus* and the coagulase-negative staphylococci) with reduced susceptibility to vancomycin (minimum inhibiting concentrations greater than 4 mg/ml) for inclusion in a central repository. A central repository of these isolates provides a standardized source of isolates for investigative studies. The strains collected for

the NARSA repository are readily available to researchers. The well-characterized isolates collected and stored in the centralized NARSA repository, together with the registry database to which they are linked, provide the general scientific community with a valuable research resource for multidisciplinary investigation. Additional information is available at [www.narsa.net/content/home.jsp](http://www.narsa.net/content/home.jsp).

### *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense

The *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program provides a broad range of preclinical developmental resources for product development and clinical testing. The areas of this contract include *in vitro* screening for antimicrobial activity, clinical isolate panels for selected bacterial pathogens, small animal models, nonhuman primate models and studies, safety/toxicology and immunogenicity testing for vaccines, and safety/toxicology and pharmacology testing for therapeutics.

### Biodefense and Emerging Infectious Diseases Research Resources Program

The Biodefense and Emerging Infectious Diseases Research Resource Program acquires, authenticates, stores, and distributes state-of-the-art research and reference reagents and standardized panels to the scientific community. This resource, funded in 2003, includes the capability to validate, expand, and produce biological agents including cell lines, clones, proteins, monoclonal and polyclonal antibodies, and diagnostic reagents and tools. The acquisition of NIAID Category A priority pathogens and reagents for research on these threat agents is a high priority.

### Pathogen Functional Genomics Resource Center (PFGRC)

PFGRC is a centralized facility that provides the research community with resources necessary to

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conduct functional genomics research on human pathogens and invertebrate vectors. PFGRC provides scientists with genomic resources and reagents such as microarrays, protein expression clones, genotyping, and bioinformatics services.

In addition, PFGRC has the capability to train scientists in the latest techniques in functional genomics and development of emerging genomic technologies. Additional information is available at <http://pfgrc.tigr.org>.

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# **COUNCIL, REVIEW COMMITTEES, AND WORKING GROUPS**



## NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

Composed of both scientists and laypersons, the National Advisory Allergy and Infectious Diseases Council makes final recommendations on the scientific merit of NIAID-assigned applications for research grants, cooperative agreements, and research training awards. Council review is the final step in the NIH peer review process, and its recommendations are based both on scientific merit, as judged by the scientific review groups, and on the relevance of the proposed study to the Institute's programs and priorities. Applications reviewed relate to all activities within the NIAID research mission, including the fields of immunology, allergic and immunologic diseases, transplantation immunology, microbiology and infectious diseases, and AIDS and AIDS-related conditions. Through its subcommittees, the Council conducts concept clearances and advises NIAID on general policy.

The National Advisory Allergy and Infectious Diseases Council roster is located at the Web site [http://www.niaid.nih.gov/ncn/budget/default\\_council.htm](http://www.niaid.nih.gov/ncn/budget/default_council.htm).

### Roster

#### **Anthony S. Fauci, M.D. (Chair)**

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## ACQUIRED IMMUNODEFICIENCY SYNDROME RESEARCH REVIEW COMMITTEE

In its role within the NIH peer review system, the Acquired Immunodeficiency Syndrome (AIDS) Research Review Committee advises the Directors of the NIH and NIAID with respect to programs and activities in the areas of AIDS as well as the prevention and treatment of the major opportunistic infections associated with AIDS. The Committee provides a primary review of selected grant applications, cooperative agreements, and contract proposals for special research and training programs. These include program projects and centers, institutional National Research Service Awards, and special developmental award programs in AIDS-related areas. The Committee recommends ratings for applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in the above-mentioned scientific areas.

The AIDS Research Review Committee roster is located at the Web site <http://www3.niaid.nih.gov/about/overview/councilcommittees/revcom.htm>.

### Roster

#### **Robert W. Doms, M.D., Ph.D. (Chair)**

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## AIDS RESEARCH ADVISORY COMMITTEE

The AIDS Research Advisory Committee is mandated by Public Law 100–607, the Health Omnibus Programs Extension of 1988 (HOPE legislation), which was signed into law November 4, 1988. The Committee advises and makes recommendations to the Director, NIAID, and to the Director, Division of Acquired Immunodeficiency Syndrome (DAIDS), in all areas of biomedical research on HIV infection and AIDS related to the mission of DAIDS, including pathogenesis, natural history, and transmission of HIV disease, and to those efforts that support progress in the detection, treatment, and prevention of HIV disease.

The Committee provides broad scientific, programmatic, and budgetary advice on all aspects of HIV-related research supported by NIAID, including fundamental basic and clinical research, discovery and development of vaccines and other preventive interventions, and training of researchers in these activities. The Committee's activity includes the review of progress and productivity of ongoing efforts, assistance in identifying critical gaps/obstacles to progress, and approval of concepts for new initiatives.

The AIDS Research Advisory Committee Roster is located at the Web site <http://www3.niaid.nih.gov/about/overview/councilcommittees/arac.htm>.

### Roster

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## AIDS VACCINE RESEARCH WORKING GROUP

The AIDS Vaccine Research Working Group, established in February 1997, assists in developing a comprehensive research program for expediting the discovery and development of an HIV vaccine. The individuals in this group provide advice regarding the vaccine research programs at the NIH with respect to scientific opportunities, gaps in knowledge, and future directions of research. The Working Group, which reports to the NIAID Council, is chaired by Scott Hammer, M.D., and is composed of individuals with expertise in immunology, structural biology, virology, animal models, and vaccine development.

The AIDS Vaccine Research Working Group roster is located at the Web site [www.niaid.nih.gov/daids/vaccine/AVRCR.htm](http://www.niaid.nih.gov/daids/vaccine/AVRCR.htm).

### Roster

#### **Scott Hammer, M.D. (Chair)**

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 Division of AIDS  
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## ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION RESEARCH COMMITTEE

The Allergy, Immunology, and Transplantation Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in the areas of allergy, clinical immunology, immunopathology, immunobiology, immunogenetics, immunochemistry, and transplantation biology. The Committee provides primary review of grant applications and special research programs. These include program projects, institutional National Research Service Awards, and special developmental award programs. The Committee recommends ratings for the applications that it determines to have significant and substantial scientific merit.

The Allergy, Immunology, and Transplantation Research Committee roster is located online at [http://www3.niaid.nih.gov/about/overview/councilcommittees/AIT\\_Research\\_Committee.htm](http://www3.niaid.nih.gov/about/overview/councilcommittees/AIT_Research_Committee.htm).

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 National Institute of Allergy and Infectious  
 Diseases  
 National Institutes of Health  
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## MICROBIOLOGY AND INFECTIOUS DISEASES RESEARCH COMMITTEE

The Microbiology and Infectious Diseases Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in microbiology and infectious diseases. Specialized areas of concern include molecular biology, microbial chemistry, parasitology, virology, bacteriology, mycology, vaccine development, and antimicrobial chemotherapy. The Committee provides a primary review of grant applications, cooperative agreements, and contract proposals for special research programs. These include program projects and centers, institutional National Research Service Awards, and special developmental award programs in the areas mentioned above. The Committee recommends ratings for applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in these scientific areas.

The Microbiology and Infectious Diseases Research Committee roster is located online at [http://www3.niaid.nih.gov/about/overview/councilcommittees/MID\\_Review\\_Committee.htm](http://www3.niaid.nih.gov/about/overview/councilcommittees/MID_Review_Committee.htm).

### Roster

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 Department of Internal Medicine  
 College of Osteopathic Medicine  
 Michigan State University  
 East Lansing, MI 48824  
 (Term expires June 30, 2008)

**Scientific Review Administrator**

**Annie Walker-Abbey, Ph.D.**

Division of Extramural Activities  
 National Institute of Allergy and Infectious  
 Diseases  
 National Institutes of Health  
 Bethesda, MD 20892

## BOARD OF SCIENTIFIC COUNSELORS

The Board of Scientific Counselors advises the Director, NIH; the Deputy Director for Intramural Research, NIH; the Director, NIAID; and the Director, Division of Intramural Research (DIR), NIAID, concerning the Institute's intramural research programs. The Board's recommendations are based on rigid and objective reviews of NIAID laboratories to assess ongoing research as well as future directions and to evaluate the productivity and performance of NIAID's tenured scientists and tenure-track scientists. Following each review, the written report from the Board is forwarded, with a response from the Director, DIR, NIAID, to the Deputy Director for Intramural Research, NIH. In addition, the Board's recommendations are communicated annually to the National Advisory Allergy and Infectious Diseases Council.

The Board's review process strengthens NIAID's tenure system and the overall quality of the Institute's research. As a result of the Board's scientific review, NIAID can modify or redirect its intramural research priorities to allow for scientific growth of investigators as well as pursuit of important new areas of research. Its findings have a direct impact on the allocation of personnel, budget, and space resources within each laboratory.

The Board of Scientific Counselors roster is located at the Web site <http://www3.niaid.nih.gov/about/overview/councilcommittees/bscroste.htm>.

### Roster

#### **Barbara A. Osborne, Ph.D. (Chair)**

*Professor*  
Department of Veterinary and Animal Sciences  
University of Massachusetts  
Amherst, MA 01003  
(Term expired June 30, 2005)

#### **Richard J. Whitley, M.D. (Co-chair)**

*Loeb Chair in Pediatrics*  
Professor of Pediatrics, Microbiology, and  
Medicine  
Department of Pediatrics  
Children's Hospital  
University of Alabama at Birmingham  
Birmingham, AL 35233  
(Term expired June 30, 2005)

#### **Robert L. Coffman, Ph.D.**

Dynavax Technologies  
717 Potter Street, Suite 100  
Berkeley, CA 94710  
(Term expires June 30, 2009)

#### **Mary K. Estes, Ph.D.**

*Professor*  
Department of Molecular Virology and  
Microbiology  
Baylor College of Medicine  
Houston, TX 77030  
(Term expires June 30, 2009)

#### **Scott Koenig, M.D., Ph.D.**

*President and Chief Executive Officer*  
MacroGenics, Inc.  
Rockville, MD 20850  
(Term expires June 30, 2008)

#### **Steven L. Kunkel, Ph.D.**

*Endowed Professor of Pathology Research*  
*Co-director*  
Division of General Pathology  
Department of Pathology  
University of Michigan  
Ann Arbor, MI 48109-0602  
(Term expires June 30, 2008)

**David M. Mosser, Ph.D.**

*Professor*

Cell Biology and Molecular Genetics  
 University of Maryland  
 College Park, MD 20742  
 (Term expires June 30, 2009)

**Charles M. Rice, Ph.D.**

*Maurice R. and Corinne P. Greenberg Professor*  
 Laboratory of Virology and Infectious Disease  
 Center for the Study of Hepatitis C  
 Rockefeller University  
 New York, NY 10021  
 (Term expires June 30, 2009)

**Laurence A. Turka, M.D.**

*C. Mahlon Kline Professor of Medicine*  
 University of Pennsylvania  
 Philadelphia, PA 19104  
 (Term expires June 30, 2007)

**Janis J. Weis, Ph.D.**

*Professor*

Division of Cell Biology and Immunology  
 Department of Pathology  
 University of Utah School of Medicine  
 Salt Lake City, UT 84132  
 (Term expires June 30, 2007)

**Executive Secretary**

**Kathryn Zoon, Ph.D.**

*Director*

Division of Intramural Research  
 National Institute of Allergy and Infectious  
 Diseases  
 National Institutes of Health  
 Bethesda, MD 20892

## VRC SUBCOMMITTEE OF THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES BOARD OF SCIENTIFIC COUNSELORS

The Vaccine Research Center (VRC) Board of Scientific Counselors (BSC) subcommittee has been established and consists of 10 members: 5 members serving for 3-year terms, and 5 members serving for 5-year terms. A quorum for this subcommittee consists of the presence of six members. The VRC BSC anticipates holding meetings once yearly.

The VRC BSC subcommittee has been charged with carrying out technical and scientific peer review of research conducted at the VRC, including: general aims, objectives, and importance of research projects; projected directions of VRC research and future research projects; and productivity and performance of VRC laboratories under review.

### Roster

#### **Rafi Ahmed, Ph.D.**

*Director*  
Emory Vaccine Center  
Emory School of Medicine  
Atlanta, GA 30322

#### **Nina Bhardwaj, M.D., Ph.D.**

*Professor*  
Departments of Medicine (Cancer Center), and  
Pathology and Dermatology  
*Director*  
Tumor Vaccine Program  
New York University  
New York, NY 10003

#### **Raphael Dolin, M.D.**

*Maxwell Finland Professor of Medicine*  
*Dean*  
Academic and Clinical Programs  
Harvard Medical School  
Boston, MA 02115

#### **Shiu-Lok Hu, Ph.D.**

*Professor*  
Department of Pharmaceutics and Microbiology  
Washington National Primate Research Center,  
Core Staff  
University of Washington  
Seattle, WA 98195

#### **Myron Levine, M.D.**

*Professor and Head*  
Division of Infectious Diseases and Tropical  
Pediatrics  
University of Maryland School of Medicine  
Baltimore, MD 21201

#### **David Montefiori, Ph.D.**

*Research Professor*  
Surgical Virology Laboratory  
Duke University Medical Center  
Durham, NC 27706

#### **Neal Nathanson, Ph.D.**

*Professor Emeritus*  
Department of Microbiology  
University of Pennsylvania  
Philadelphia, PA 19104

#### **Quentin Sattentau, Ph.D.**

*Reader in Immunology*  
Department of Pathology  
Magdalen College  
University of Oxford  
Oxford, UK OX1 4AU

#### **Robert Schooley, M.D.**

*Director*  
Colorado Center for AIDS Research  
Coordinator for International Programs  
University of Colorado Health Sciences Center  
Denver, CO 80262

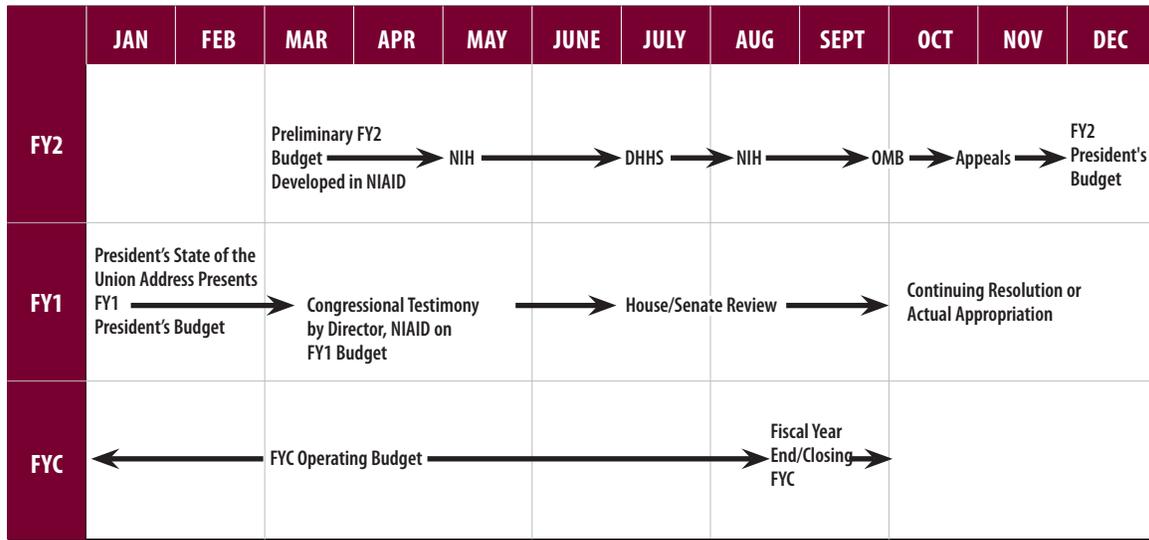
#### **George Siber, M.D.**

*Executive Vice President and Chief Scientific Officer*  
Wyeth Vaccines  
Pearl River, NY 10965

# **BUDGET OVERVIEW AND HISTORICAL TRENDS**



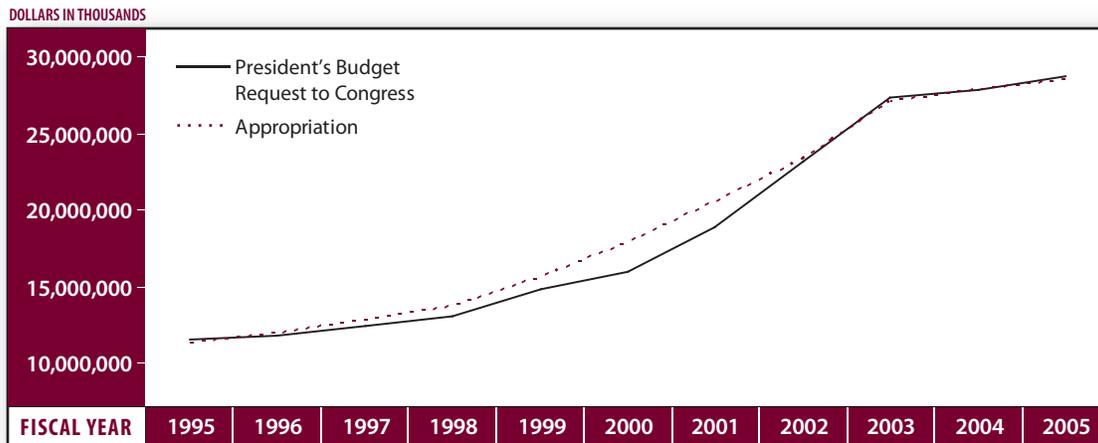
## FEDERAL BUDGET PROCESS



**FISCAL YEAR** = OCTOBER 1 TO SEPTEMBER 30

- FY1** = FIRST FUTURE FISCAL YEAR
- FY2** = SECOND FUTURE FISCAL YEAR
- FYC** = CURRENT FISCAL YEAR

## NIH APPROPRIATIONS HISTORY: FY 1995–2005



Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation <sup>a</sup>
<i>(Dollars in Thousands)</i>				
1995	11,473,000	11,322,023	11,333,181	11,299,522 <sup>b</sup>
1996	11,773,066	11,939,001	11,639,204	11,927,562 <sup>c</sup>
1997	12,406,300 <sup>d</sup>	12,747,203	12,414,580 <sup>e</sup>	12,740,843 <sup>f</sup>
1998	13,078,203 <sup>g</sup>	13,505,294	13,692,844	13,674,843 <sup>h, i</sup>
1999	14,763,313 <sup>j</sup>	14,862,023	15,622,386	15,629,156 <sup>k</sup>
2000	15,932,786	16,964,547	17,613,470	17,820,587 <sup>l</sup>
2001	18,812,735	20,512,735	20,512,735	20,458,130 <sup>m, n</sup>
2002	23,112,130	22,945,199	23,765,488	23,296,382 <sup>o, p</sup>
2003	27,343,417 <sup>q, r</sup>	27,351,717	27,369,000 <sup>s</sup>	27,066,782 <sup>t</sup>
2004	27,892,765 <sup>r</sup>	26,043,991	28,369,548	27,887,512 <sup>u</sup>
2005	28,757,357	28,657,357	28,901,185	28,495,157 <sup>v</sup>

a Reflects enacted supplements, rescissions, and reappropriations.

b Includes \$1,299,328 for NIH research appropriated to the NIH Office of AIDS Research. Reflects enacted reductions of \$7,446 for procurement, \$345,000 for rent, and \$4,401 for bonus pay, and rescission of \$10,000 in NCRF for construction and \$12,384 in administrative costs.

c Includes \$1,410,925 appropriated to the ICs for HIV research. Incorporates the NIH share of the Government-wide administrative cost rescission (\$5,780) and the Labor/HHS/Education bonus pay rescission (\$5,659).

d Includes \$1,431,908 for HIV research in the NIH Office of AIDS Research.

e Includes \$1,460,312 for HIV research in the NIH Office of AIDS Research.

f Includes \$1,501,073 for HIV research in the NIH Office of AIDS Research. Incorporated the NIH share of the salaries and expenses reduction (\$6,140) and the public/legislative affairs reduction (\$220).

g Includes \$1,540,765 for HIV research in the NIH Office of AIDS Research.

h Includes \$1,607,053 appropriated to the ICs for HIV research.

i Beginning in FY 1998, the appropriation includes funds appropriated to NIDDK for type 1 diabetes research.

j Reflects a decrease of \$34,530 for the budget amendment for bioterrorism. Includes \$1,728,099 for HIV research in the NIH Office of AIDS research.

k Includes \$1,800,046 appropriated to the ICs for HIV research. Includes rescission of \$10,230.

l Includes \$2,024,956 appropriated to the ICs for HIV research. Includes \$99,883 for NIH share of across-the-board reduction and reflects \$20,000 transferred to CDC. Includes \$40,000 in forward funding appropriated in FY 1999.

m Includes \$2,244,987 appropriated to ICs for HIV research. Reflects NIH share of across-the-board reduction (\$8,666) and \$5,800 transferred to the DHHS.

n Beginning in FY 2001, VA/HUD began appropriating Superfund Research funds directly to NIEHS.

o Includes \$2,535,672 appropriated to the ICs for HIV research. Reflects NIH share of across-the-board reduction (\$9,273) and transfer for \$100 million to the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis.

p Includes \$10.5 million appropriated from the Emergency Relief Fund.

q Excludes \$583 transferred to the Department of Homeland Security.

r Includes \$100 million in FY 2003 and \$150 million in FY 2004 and FY 2005 authorized to NIDDK for type 1 diabetes research.

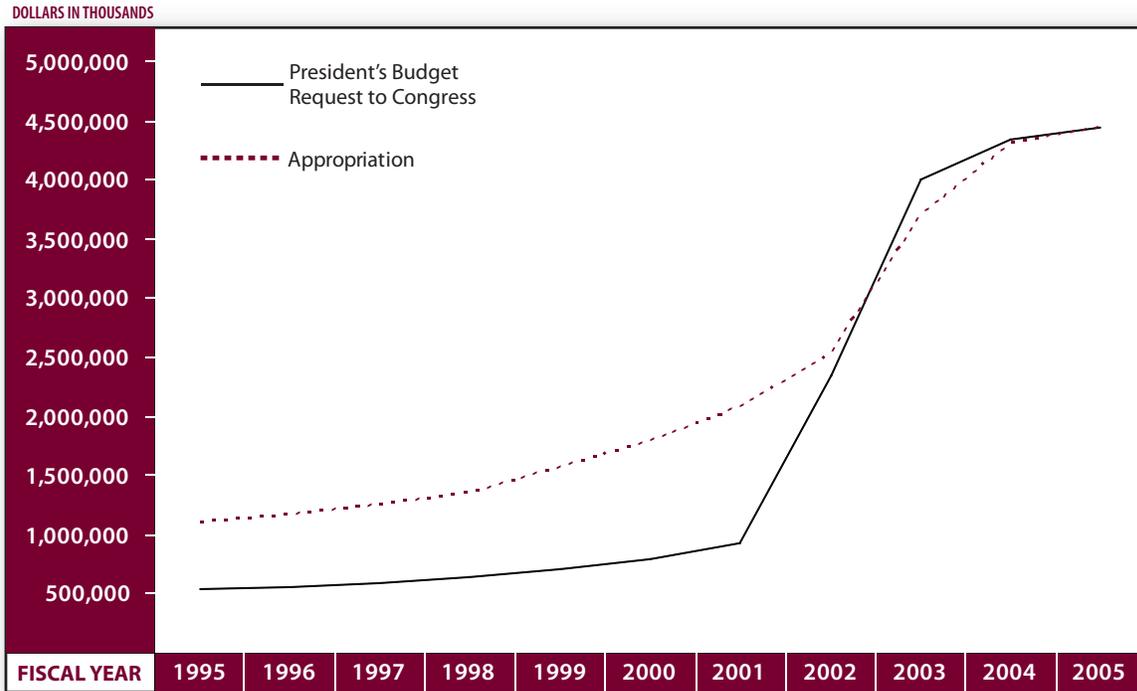
s Includes \$97 million authorized to NIDDK for type 1 diabetes research.

t Includes \$2,747,463 appropriated to the ICs for HIV research. Reflects NIH share of the across-the-board reduction (\$177,085), and transfers of \$99,350 to the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis, and \$583,000 to the Department of Homeland Security.

u Includes \$2,850,581 appropriated to the ICs for HIV research. Reflects NIH share of the across-the-board reduction (\$165,459), Labor/HHS rescission (\$17,492), and transfer of \$149,115 to the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis.

v Includes \$2,920,551 appropriated to the ICs for HIV research. Reflects NIH share of across-the-board reduction (\$229,390), Labor/HHS rescission (\$6,787), and transfer of \$99,200 to the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis.

## NIAID APPROPRIATIONS HISTORY: FY 1995–2005



Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation <sup>a</sup>
<i>(Dollars in Thousands)</i>				
1995	542,864 <sup>b</sup>	1,094,633	1,094,633	1,092,507 <sup>c</sup>
1996	557,354 <sup>b</sup>	1,169,628	1,139,326	1,171,168 <sup>d</sup>
1997	584,362 <sup>b</sup>	1,256,149	1,229,009	1,257,794 <sup>e</sup>
1998	634,272 <sup>b</sup>	1,339,459	1,359,688	1,352,119 <sup>f</sup>
1999	703,723 <sup>b,g</sup>	1,470,460	1,540,102	1,569,063
2000	789,156	1,694,019	1,786,718	1,797,988 <sup>h</sup>
2001	936,166	2,062,126 <sup>i</sup>	2,066,526	2,069,388
2002	2,355,325	2,337,204	2,375,836	2,535,788
2003	3,997,369	2,674,213	3,727,473	3,706,789
2004	4,335,255	4,440,007 <sup>j</sup>	4,456,300 <sup>k</sup>	4,303,040 <sup>l</sup>
2005	4,440,007	4,440,007	4,456,300	4,440,007

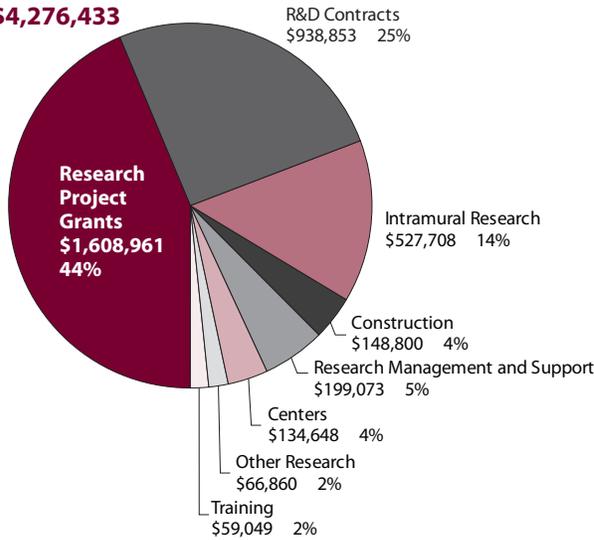
- a Reflects enacted supplements, rescissions, and reappropriations.
- b Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
- c Includes a rescission of \$1,293,000 and a transfer of \$458,000.
- d Includes an enacted administrative reduction of \$1,145,000 and a net NIH Director's transfer of \$2,685.
- e Includes a rescission of \$575,000 for administrative expenses and a net positive transfer of \$1,135,000 from the NIH Director's Reserve.
- f Includes rescissions and transfers.

- g Reflects an increase of \$1,683,000 for the budget amendment for biodefense.
- h Includes a rescission of \$5,075,000.
- i Represents program level.
- j Includes \$100M for the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis and \$14.5M for the Virtual VRC.
- k Includes \$149M for the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis and \$14.5M for the Virtual VRC.
- l Includes \$149M for the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis.

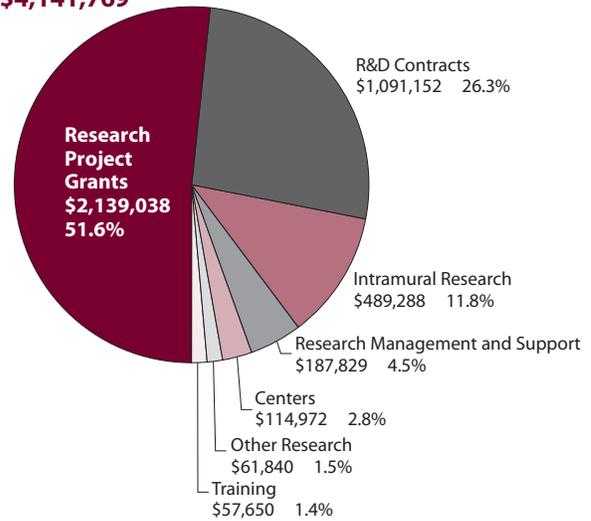
## NIAID FUNDING BY BUDGET MECHANISM: FY 2004–2005

(Dollars in Thousands)

**Fiscal Year 2005**  
**\$4,276,433**



**Fiscal Year 2004**  
**\$4,141,769**

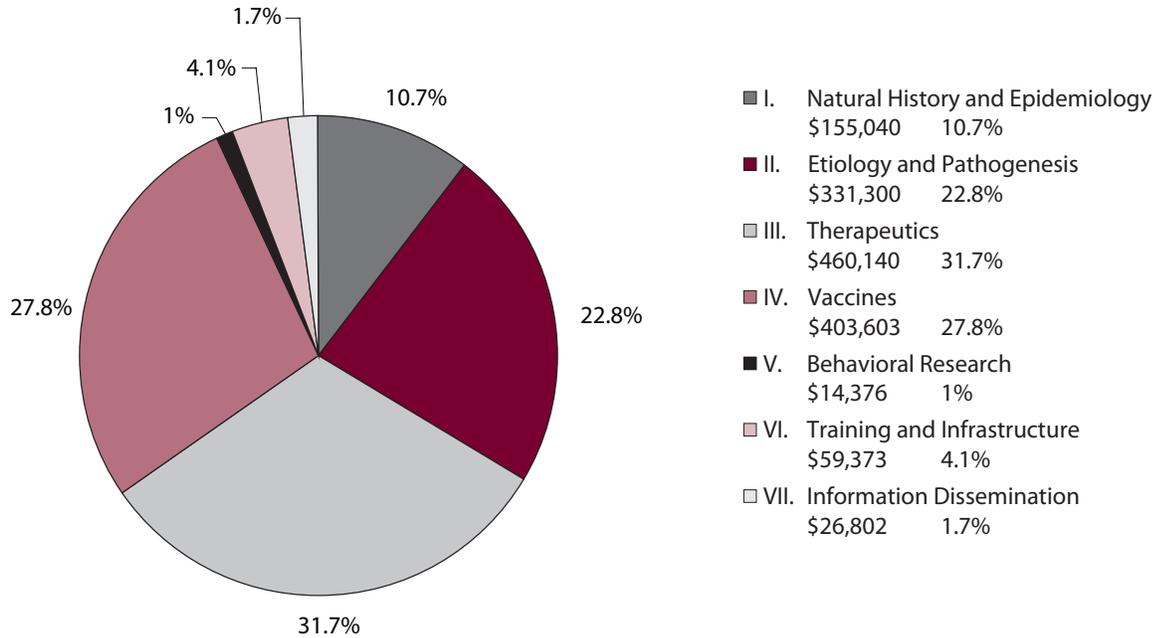


Budget Mechanism	FY 2004 <sup>a</sup>	% of Total	FY 2005 <sup>a</sup>	% of Total	% Change FY04 to FY05
Research Project Grants (RPGs)					
Noncompeting	\$1,486,283		\$1,608,961		
Competing	652,755		592,481		
Subtotal, RPGs	2,139,038	51.6	2,201,442	51.5	-0.1
Centers	114,972	2.8	134,648	3.1	+0.3
Other Research	61,840	1.5	66,860	1.6	+0.1
Training	57,650	1.4	59,049	1.4	0
R&D Contracts	1,091,152	26.3	938,853	22.0	-4.3
Subtotal, Extramural	3,464,652		3,400,852		
Intramural Research	489,288	11.8	527,708	12.3	+0.5
Research Management and Support	187,829	4.5	199,073	4.7	+0.2
Construction	0	0	148,800	3.5	
<b>Total</b>	<b>\$4,141,769</b>		<b>\$4,276,433</b>		<b>+3.3</b>

<sup>a</sup> Dollars in thousands and reflects actual obligations.

## NIAID FUNDING BY THE FY 2005 NIH PLAN FOR HIV-RELATED RESEARCH<sup>a</sup> (Dollars in Thousands)

**Total Funding by the FY 2005 Plan  
\$1,450,634**

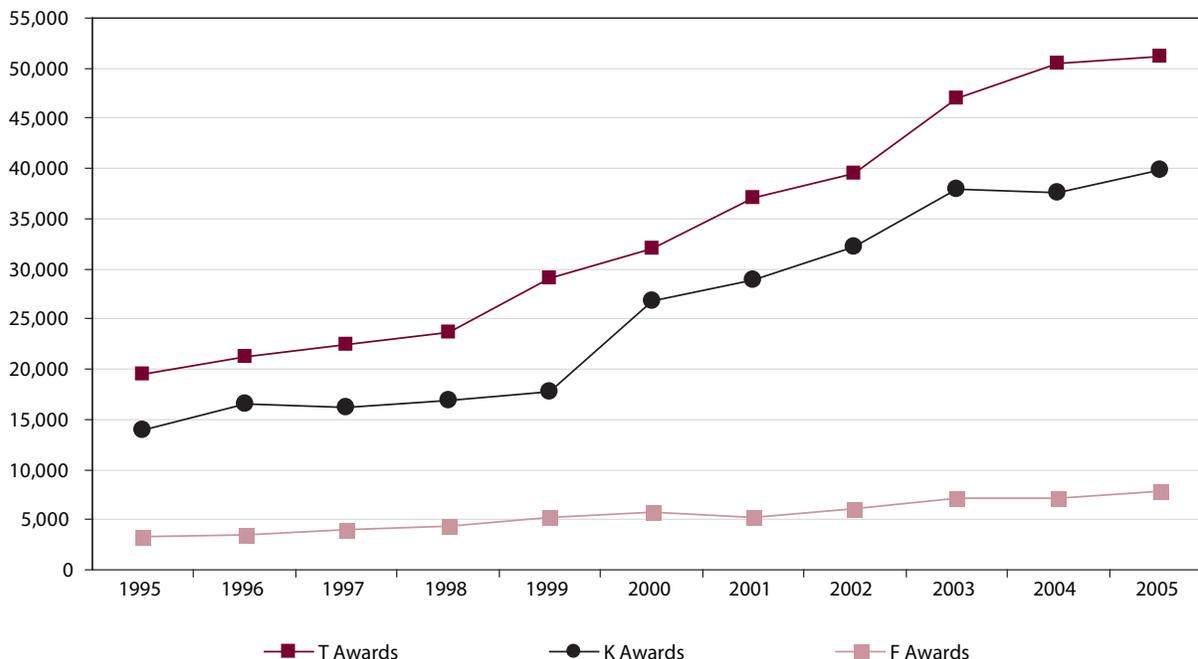


	FY 2005 Actual	
	Amount	Percent of Total
I. Natural History and Epidemiology	\$155,040	10.7%
II. Etiology and Pathogenesis	331,300	22.8%
III. Therapeutics	460,140	31.7%
IV. Vaccines	403,603	27.8%
V. Behavioral Research	14,376	1%
VI. Training and Infrastructure	59,373	4.1%
VII. Information Dissemination	26,802	1.7%
<b>Total Funding by the FY 2005 Plan</b>	<b>\$1,450,634</b>	<b>100%</b>

<sup>a</sup> A comprehensive plan for HIV-related research developed by the NIH Office of AIDS Research and the NIH Institutes and Centers.

## NIAID RESEARCH TRAINING AND CAREER AWARDS<sup>a</sup> : FY 1995–2005

(Dollars in Thousands)



Fiscal Year	T Awards (Institutional Awards)		K Awards (Career Awards)		F Awards (Individual Training Awards)	
	No. Awards	Dollar Amount	No. Awards	Dollar Amount	No. Awards	Dollar Amount
1995	118	19,539	176	13,884	124	3,386
1996	123	21,254	204	16,566	126	3,439
1997	140	22,478	204	16,159	150	4,067
1998	152	23,738	211	16,908	151	4,350
1999	148	29,092	205	17,686	146	5,177
2000	164	32,035	241	26,863	161	5,709
2001	923	37,113	245	28,885	146	5,266
2002	919	39,474	272	32,237	153	6,162
2003	1,014	46,936	309	38,030	163	7,108
2004	1,087	50,550	314	37,521	173	7,100
2005	1,078	51,136	326	39,903	187	7,913

<sup>a</sup> Includes F31, F32, F33, F34, K04, K06, K07, K08, K11, T32, T35, and T36 awards (described in the NIH Extramural Funding Mechanisms appendix).

# APPENDICES



## APPENDICES

## LEGISLATIVE CHRONOLOGY

**NOV. 1, 1948**

The National Microbiological Institute was established under authority of section 202 of the Public Health Service Act, as implemented by General Circular No. 55, Organization Order No. 20, dated October 8, 1948.

**DEC. 29, 1955**

NIAID was established (replacing the National Microbiological Institute) under authority of the Omnibus Medical Research Act (Public Law 81-692, 64 Stat. L. 443), as implemented by a Public Health Service Briefing Memorandum of November 4, 1955, from the Surgeon General to the Secretary of Health, Education, and Welfare.

**NOV. 4, 1988**

NIAID was provided with additional authorities for AIDS research under Title II of the Health Omnibus Programs Extension of 1988 (HOPE legislation) (Public Law 100-07), the first major law to address AIDS research, information, education, and prevention.

**AUG. 14, 1991**

The Public Health Service Act was amended by Public Law 102-96, the Terry Beirn Community-Based AIDS Research Initiative Act of 1991, which reauthorized NIAID's Community Programs for Clinical Research on AIDS (CPCRA). CPCRA was renamed in honor of Mr. Beirn (an AIDS activist and congressional staffer who died in 1991) and was reauthorized for an additional 5 years.

**JUNE 10, 1993**

The Public Health Service Act was amended by Public Law 103-43, the National Institutes of Health Revitalization Act of 1993. This comprehensive legislation required NIAID to include research on tropical diseases in its mission statement and directs the Secretary, U.S. Department of Health and Human Services, to ensure that individuals with expertise in chronic fatigue syndrome or neuromuscular diseases are appointed to appropriate NIH advisory committees.

**DEC. 14, 1993**

The Preventive Health Amendments of 1993 were passed, which included provisions requiring the Director, NIAID, to conduct or support research and research training regarding the cause, early detection, prevention, and treatment of tuberculosis. (The Institute already had authority to conduct such research under its authorities in Title IV, Public Health Service Act.)

**NOV. 29, 1999**

The fiscal year 2000 Appropriations Act (Public Law 106-113) established the NIH Challenge Grants program to promote joint ventures between the NIH and the biotechnology, pharmaceutical, and medical device industries. A one-time funding level of \$20 million was provided within the Public Health and Social Services Emergency Fund.

**OCT. 17, 2000**

The Children's Health Act (Public Law 106-310) required the Directors of NIAID and the National Institute of Arthritis and Musculoskeletal and Skin Diseases to expand and intensify the activities of their Institutes with respect to research and related activities concerning juvenile arthritis and related conditions.

**NOV. 13, 2000**

The Public Health Improvement Act (Public Law 106-505) authorized the NIAID Director to establish a program of clinical research and training awards for sexually transmitted infections.

**July 21, 2004**

The Project Bioshield Act (Public Law 108-276) authorized the Director of NIH to employ expedited peer review procedures for grants, contracts, and cooperative agreements addressing qualified countermeasures research. In addition, the Act authorized the Director of NIAID to award grants or contracts to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new facilities.

**Previous Directors**

Victor H. Haas, M.D., 1948–1957

Justin M. Andrews, Sc.D., 1957–1964

Dorland J. Davis, M.D., D.P.H., 1964–1975

Richard M. Krause, M.D., 1975–1984

## TECHNOLOGY TRANSFER

Technology transfer in Federal laboratories facilitates the dissemination of new technologies and research materials developed by Government scientists. This technology transfer fuels further innovation and commercialization by the extramural research and development community, ultimately resulting in improved public health and increased competitiveness by U.S. industry. Federal legislation mandates and defines the Government's technology transfer activities. The key pieces of legislation are the Federal Technology Transfer Act of 1986 and the National Technology Transfer and Advancement Act of 1995.

The NIAID Office of Technology Development (OTD) accomplishes technology transfer by facilitating the transfer of significant research advances and resources to the broader scientific community and promoting development of collaborative relationships among NIAID scientists, industry, and academia. NIAID uses various mechanisms to accomplish these ends, including Material Transfer Agreements (MTAs), Cooperative Research and Development Agreements (CRADAs), Materials-CRADAs (M-CRADAs), Confidential Disclosure Agreements (CDAs), Clinical Trial Agreements (CTAs), Drug Screening Agreements, Research Collaboration Agreements (RCAs), and, through the NIH Office of Technology Transfer (OTT), patenting of inventions and negotiation of various license agreements.

NIAID scientists report inventions to OTD by submitting Employee Invention Reports (EIRs). The EIRs are reviewed by OTD and, with the assistance of the NIAID Technology Evaluation Advisory Committee (TEAC), are evaluated for the appropriateness of filing domestic and foreign patent applications. In FY 2005, TEAC reviewed 36 EIRs and recommended that patent applications be filed on 23 of them. At the end of FY 2005, NIAID had 422 active U.S. patent

properties, including 213 issued patents and 209 pending patent applications.

NIAID had a total of 245 active license agreements at the end of FY 2005 for both patented inventions and biological materials. Fifty-eight new licenses were executed during FY 2005. These licenses generated about \$14.5 million in royalty income, which was first used to pay NIAID inventors their share according to Federal law and NIH policy. The Institute also distributed royalty income to intramural laboratories to support research projects and equipment acquisition that otherwise would not have been accomplished with appropriated funds. The remaining royalties were used to pay OTD's entire operating budget, including patent prosecution fees, staff salaries, associated office expenses, and overhead charged by OTT.

In FY 2005, a total of 149 MTAs (of which 17 were with for-profit companies), 9 CTAs, 92 CDAs, 4 CRADAs, 12 M-CRADAs, 8 RCAs, and 15 other agreements were negotiated by OTD and executed. NIAID extramural divisions referred technology transfer issues to OTD on 23 contracts, and OTD NIAID scientists performed research under 28 CRADAs and 38 M-CRADAs in FY 2005. The following table provides a history of NIAID's patent, license, and CRADA activities.

### NIAID Technology Transfer Activities

Fiscal Year	Pending Patents	Issued Patents	Licenses In Effect	Active CRADAs
1992	77	48	65	21
1994	85	65	84	29
1995	96	71	101	31
1996	95	84	120	42
1997	128	91	131	71
1998	154	83	155	95
1999	169	94	195	74
2000	229	100	196	86
2001	194	125	190	93
2002	147	139	197	85
2003	174	168	245	71
2004	177	209	226	70
2005	212	255	270	76

## Technology Transfer Highlights

In FY 2005, OTD negotiated or facilitated the following public-private partnerships:

- **Development of Live-Attenuated Vaccines for Pandemic Influenza. (MedImmune)**

The emergence of new strains of influenza infectious to humans is recognized globally as a genuine public health concern. Although the specific location or source of an outbreak cannot be precisely predicted, there is worldwide recognition that such an occurrence could be devastating to human populations. NIAID will collaborate under this CRADA with MedImmune Vaccines to use genetic techniques to develop vaccines against potential pandemic strains of influenza. The NIAID/MedImmune partnership was announced in September 2005. For more details, see [www3.niaid.nih.gov/news/newsreleases/2005/medimmune.htm](http://www3.niaid.nih.gov/news/newsreleases/2005/medimmune.htm).

- **Genome Integration Site Analysis Following *Ex Vivo* Transduction of Hematopoietic Stem/Progenitor Cells by Replication Incompetent Retrovirus Vectors. (Johnson and Johnson Research Pty Limited)** NIAID and Johnson and Johnson Research Pty Limited will determine the pattern of distribution of retrovirus vector insert sites in the genome of human hematopoietic progenitor cells that are transduced with retrovirus vectors that have been used in the past by each of the groups for *ex vivo* gene transfer targeting human hematopoietic progenitor cells. This is relevant to the important safety issue of determining the risk of cancer induction (insertional oncogenesis) associated with

*ex vivo* gene transfer targeting human hematopoietic progenitor cells. The study will determine whether particular genes or locations within genes are targeted in hematopoietic progenitor cells with different marrow reconstitution potential and whether the pattern is different in different retrovirus vectors. Such knowledge could not only allow assessment of risk, but could guide changes in vector design and/or *ex vivo* transduction conditions that might reduce the risk of insertion-site-mediated oncogenesis.

- **Development of Procedures to Validate, Reagents, Assays, and Instrumentation for Measuring Immunogenicity. (ReaMetrix)**

Under this CRADA, investigators in the ImmunoTechnology Section of the Vaccine Research Center (VRC) at NIAID and ReaMetrix will devise standardized technology for the validation and implementation of complex immune assays, with the development of a novel high-throughput imaging-based cytotoxicity assay as a core project.

- **Development of Electroporation (EP) or Prophylactic Therapeutic HIV Plasmid DNA (pDNA) Vaccines. (Vical)**

Investigators at the NIAID VRC and Vical, Inc., will collaborate in the development and evaluation of HIV DNA vaccine candidates. The VRC and Vical will evaluate electroporation as a means of delivery that could enhance or improve the immune response to HIV and select the best constructs and formulations of HIV DNA vaccine candidates appropriate for clinical development.

## New CRADAs

During FY 2005, NIAID scientists entered into the following four new CRADAs:

Collaborator	Investigator	Title
Johnson and Johnson Research (Australia)	Harry Malech, M.D. Laboratory of Host Defenses	Genome Integration Site Analysis Following <i>Ex Vivo</i> Transduction of Hematopoietic Stem/Progenitor Cells by Replication Incompetent Retrovirus Vectors
MedImmune	Kanta Subbarao, M.B.B.S., M.P.H. Laboratory of Infectious Diseases	Development of Live-Attenuated Vaccines for Pandemic Influenza
ReaMetrix	Mario Roederer, Ph.D. Vaccine Research Center	Development of Procedures to Validate, Reagents, Assays, and Instrumentation for Measuring Immunogenicity
Vical	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Development of EP or Prophylactic Therapeutic HIV pDNA Vaccines

## Ongoing CRADAs

In addition to the new CRADAs listed above, during FY 2005, NIAID scientists also conducted research under the following CRADAs:

Collaborator	Investigator	Title
Anacor Pharmaceuticals	Clifton E. Barry III, Ph.D. Laboratory of Immunogenetics	<i>In Vitro</i> and <i>In Vivo</i> screening of Novel Anti-tubercular Agents
BioVex	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation of HSV Vectors Encoding HIV-1 Proteins
Chiron	Harlan D. Caldwell, Ph.D., Laboratory of Intracellular Parasites	Chlamydia Antigen Discovery
Chiron	H. Clifford Lane, M.D. Laboratory of Immunoregulation	Research and Development of IL-2 as a Treatment for HIV Infection
Crucell	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Development of an Improved Recombinant Adenovirus Vector for Vaccination Against the Ebola Virus
Genetics Institute	Ethan Shevach, M.D. Laboratory of Immunology	Analysis of Gene Expression in Immunoregulatory T Cells that Co-express the CD4 and CD25 Surface Markers
GenVec	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation of Adenoviral Vectors Encoding HIV-1 Proteins
GenVec	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation of Adenoviral Vectors Encoding Proteins Associated with SARS
GlaxoSmithKline	Holli Hamilton, M.D., M.P.H. Barbara Savarese, R.N. Division of Microbiology and Infectious Diseases	A Double-Blind, Randomized, Controlled Phase III Study to Assess the Prophylactic Efficacy of rgD/Alum/MPL Vaccine in the Prevention of Genital Herpes Disease in Young Sexually Active Women (DMID#01–643)
Ichor Medical Systems	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation of Electroporation-Mediated Delivery of an HIV DNA Vaccine

Collaborator	Investigator	Title
Innogenetics	Robert H. Purcell, M.D. Laboratory of Infectious Diseases	Analysis of the Immune Response to Hepatitis C Virus
Invitrogen	Thomas Kindt, Ph.D. Michael Wilson, Ph.D. Research Technologies Branch, Division of Intramural Research	Oligonucleotide Control Sets for Microarray Applications
MacroGenics, Inc.	Robert H. Purcell, M.D. Laboratory of Infectious Diseases	Development of Prophylactic and Therapeutic Monoclonal Antibodies to Vaccinia/Smallpox, SARS, and Anthrax
Maxygen	Louis Miller, M.D. Carole Long, Ph.D. Allan Saul, Ph.D. Laboratory of Parasitic Disease	Novel, Polyspecific Malaria Vaccine Development Based on PfEMP1 Using Molecular Breeding™ Directed Molecular Evolution Technologies
Merck	Gary Nabel, M.D., Ph.D. Vaccine Research Center	Development of an Adenoviral-Based HIV Vaccine
Merck	Stephen Straus, M.D. Laboratory of Clinical Investigation	A Double-Blind, Placebo-Controlled Study of the Efficacy of Live-Attenuated Oka/Merck Varicella Zoster Vaccine in Reducing the Incidence and/or Severity of Shingles in Adults
Merial	José Ribeiro M.D., Ph.D. Laboratory of Parasitic Disease	Evaluation of DNA Vaccines Encoding Sand Fly Salivary Proteins as Candidates to Control <i>Leishmania infantum</i> Infection in Dogs
Osel	Edward Berger, Ph.D. Laboratory of Viral Diseases	SCD4-17b Expressed by/on <i>Lactobacillus</i> as an Anti-HIV Topical Microbicide
Quantum Dot	Mario Roederer, Ph.D. Vaccine Research Center	Use of Quantum Dots for Improved Cellular Classification in Flow Cytometry
Vical, Inc.	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Development and Selection of Research-Grade Plasmid DNA Vectors Encoding West Nile Virus Proteins and Formulations for Potential Use as Prophylactic Vaccines in Human and Veterinary Applications
Wyeth-Lederle Vaccines	George Curlin, M.D. Division of Microbiology and Infectious Diseases	Preventing Childhood Mortality—An Efficacy Trial of a Pneumococcal Conjugate Vaccine in Upper and Central River Divisions, The Gambia

## NIH EXTRAMURAL FUNDING MECHANISMS USED BY NIAID

### Fellowship Programs

**F31** Predoctoral Individual National Research Service Award (NRSA)—provides predoctoral individuals with supervised research training in specified health and health-related areas leading toward the research degree (e.g., Ph.D.).

**F32** Postdoctoral Individual NRSA—provides postdoctoral research training to individuals to broaden their scientific background and extend their potential for research in specified health-related areas.

**F33** NRSA for Senior Fellows—provides opportunities for experienced scientists to make major changes in the direction of their research careers, to broaden their scientific background, or to acquire new research capabilities.

**F35** Intramural NRSA Individual Postdoctoral Program—supports a postdoctoral trainee in the NIH intramural program.

### Research Career Programs

**K02** Independent Scientist Award—provides support for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers.

**K08** Clinical Investigator Award—provides the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members who will pursue research aspects of categorical areas applicable to the awarding unit, and aids in filling the important academic faculty

gap in these shortage areas within health professional institutions of the country.

**K22** Career Transition Award—provides support to outstanding newly trained basic or clinical investigators to develop their independent research skills through a two-phase program: an initial period involving an intramural appointment of the NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the investigator to sustain or promote a successful research career.

**K23** Mentored Patient-Oriented Research Career Development Award—provides support for the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for a 3-year minimum up to a 5-year period of supervised study and research for clinically trained professionals who have the potential to develop into productive clinical investigators.

**K24** Midcareer Investigator Award in Patient-Oriented Research—provides support for experienced clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators.

**K25** Mentored Quantitative Research Career Development Award—supports junior faculty-level investigators with quantitative scientific and engineering backgrounds outside of biology or medicine who have the potential to integrate their expertise with biomedicine and to develop into productive investigators with a period of mentored study and research.

**K30** Clinical Research Curriculum Award (CRCA)—awarded to institutions to stimulate the inclusion of high-quality, multidisciplinary didactic training as part of the career development of clinical investigators. This award supports the development of new didactic programs in clinical research at institutions that do not offer such programs or in institutions with existing programs in clinical research. In the latter, it supports the expansion of programs or improvement in the quality of instruction.

### Research and Development-Related Contracts

**N01** Research and Development (R&D) Contract—develops or applies new knowledge or tests, screens, or evaluates a product, material, device, or component for use by the scientific community.

### Research Program Projects and Centers

**P01** Research Program Project—provides a qualified institution, on behalf of a principal investigator, with the support of a broad-based, multidisciplinary, often long-term research program with a particular major objective or theme. A program project involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain shared resources necessary for the total research effort. Each project supported under a program project grant is expected to contribute to the overall program objective.

**P30** Center Core Grant—supports shared resources and facilities for categorical research by a number of investigators

from different disciplines who provide a multidisciplinary approach to a joint research effort or from the same discipline who focus on a common research problem. Although funded independently of the center's component projects or program projects, the core grant relates integratively to them. By providing more accessible resources, this support is expected to ensure greater productivity than that obtained from the separate projects and program projects.

**P50** Specialized Center—supports any part of the full range of R&D, from basic to clinical, and may involve ancillary supportive activities, such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multidisciplinary attack on a specific disease entity or biomedical problem area. These grants differ from program project grants in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently receive continuous attention from its staff. Centers also may serve as regional or national resources for special research purposes.

### Research Project Grants and Grants Related to Research Projects

**R01** Research Project Grant (traditional)—provides support to an institution (domestic or foreign) on behalf of a principal investigator for a discrete project related to the investigator's interests and competence. Most of the research that the NIH supports is maintained through this funding mechanism. Although rare, such a grant may be awarded directly to an individual.

- R03** Small Grant—provides research support specifically limited in time and amount for studies in categorical program areas. Small grants provide flexibility for initiating studies, which are generally for preliminary short-term projects and are nonrenewable.
- R09** Scientific Evaluation—provides the chairman of an initial review group funds for operation of the initial review group.
- R13** Conference Grant—provides funding for conferences to coordinate, exchange, and disseminate information related to program interests. In general, such awards are modest and limited to participation with other organizations in the support of conferences rather than as a provision of sole support. Among the costs eligible for support are salaries, equipment rental, travel, consultant services, and supplies. Prospective applicants should inquire in advance concerning possible interest on the part of an Institute.
- R15** Academic Research Enhancement Award (AREA)—provides support to scientists at eligible domestic institutions for small-scale, new, or expanded health-related research projects, such as pilot research projects and feasibility studies; development, testing, and refinement of research techniques; secondary analysis of available data sets; and similar discrete research projects that demonstrate research capability. This award is directed toward smaller, less-prominent 4-year public and private colleges and universities that provide undergraduate training for a significant number of U.S. research scientists but have not had an adequate share in the growth of the NIH extramural program.
- R18** Research Demonstration and Dissemination Project—provides support to develop, test, and evaluate health-service activities and to foster the application of existing knowledge for the control of categorical diseases.
- R21** Exploratory/Developmental Grant—used by NIAID for bridge awards. The bridge award provides support for a limited time and amount to investigators to enable them to continue meritorious research and improve the competitiveness of future grant applications.
- R24** Resource-Related Research Project—supports research projects that will enhance the capability of resources to serve biomedical research.
- R25** Education Project—provides support to develop or implement a program in education, information, training, technical assistance, coordination, or evaluation.
- R33** Exploratory and Developmental Grants, Phase II—provide a second phase of support for innovative, exploratory, and developmental research begun as an R21 award. Only R21 awardees are eligible to apply for R33 support. Applications are accepted only in response to RFAs and PAs that specify the R33 mechanism.
- R34** Clinical Trial Planning Grant—provides support for initial development of a clinical trial, for example, establishing a research team, developing tools for managing data and overseeing the research, and developing a trial design, protocol, recruitment strategies, and procedure manuals. Only those investigators who have received the R34 planning grant are eligible to apply for the clinical trial implementation (U01) grant.

**R37** Method to Extend Research in Time (MERIT) Award—provides long-term, stable support to investigators who are likely to continue to perform in an outstanding manner and spares them the administrative burdens associated with preparing and submitting research grant applications. An initial 5-year award is accompanied by an opportunity for a 3- to 5-year extension, based on an expedited review of the accomplishments during the initial award period. Investigators may not apply for a MERIT award. NIH staff and advisors base their selection of MERIT award recipients on competing R01 applications, prepared and submitted in accordance with NIH procedures. MERIT awards are awarded to a limited number of selected investigators who have demonstrated superior competence and outstanding productivity during previous research endeavors.

### Small Business Funding Opportunities

**R41** Small Business Technology Transfer (STTR) Grant, Phase I—supports cooperative R&D projects between small business concerns and research institutions, limited in time and amount, to establish the technical merit and feasibility of ideas that have potential for commercialization. Awards are made to small business concerns only.

**R42** STTR Grant, Phase II—supports cooperative R&D projects between small business concerns and research institutions, limited in time and amount, to establish the technical merit and feasibility of ideas that have potential for commercialization. Awards are made to small business concerns only.

**R43** Small Business Innovation Research (SBIR) Grant, Phase I—enables small businesses to contribute to the R&D mission of the NIH. Phase I grants support projects, limited in time and amount, to establish the technical merit and feasibility of ideas that ultimately might lead to commercial products or services. The research must be conducted in the United States.

**R44** SBIR Grant, Phase II—enables small businesses to contribute to the R&D mission of the NIH. Phase II grants support indepth development of ideas whose feasibility has been established in Phase I and that are likely to result in commercial products or services. The research must be conducted in the United States.

### Research Training Programs

**T32** Institutional NRSA—enables institutions to grant NRSA for predoctoral and postdoctoral research training in specified shortage areas to individuals selected by the institutions.

**T35** NRSA Short-Term Research Training—provides individuals with research training during off-quarters or summer periods to encourage research careers or research in areas of national need.

### Cooperative Agreements

**U01** Research Project (Cooperative Agreement)—provides an assistance relationship between NIH and a recipient, but with substantial programmatic involvement by NIH. NIH assists, supports, or stimulates the recipients and is involved substantially with recipients in conducting projects similar in program content to those for

grants, with NIH playing a “partner” role in the effort.

- U19** Research Program (Cooperative Agreement)—supports a research program of multiple projects directed toward a specific major objective, basic theme, or program goal that requires a broad-based, multidisciplinary, and often long-term approach.
- U24** Resource-Related Research Projects/ Cooperative Agreements—support research projects contributing to improvement of the capability of resources to serve biomedical research.
- U42** Animal (Mammalian and Nonmammalian) Model and Animal and Biomedical Materials Resource Cooperative Agreements (National Center for Research Resources)—develop and support an animal (mammalian and nonmammalian) model or animal or biological materials resources available to all qualified investigators without regard to the scientific disciplines or disease orientations of their research activities or specifically directed to a categorical program. Nonmammalian resources include nonmammalian vertebrates, invertebrates, cell systems, and nonbiological systems.
- U54** Specialized Centers Cooperative Agreements—support research and development from basic to clinical, including ancillary supportive activities that create a multidisciplinary focus on a disease or a biomedical problem. Centers also can serve as regional or national resources for special research purposes.

**U56** Exploratory Grants Cooperative Agreements—support planning for new programs, expansion or modification of existing resources, and feasibility studies for interdisciplinary programs that can lead to specialized or comprehensive centers.

**UC1** NIH Challenge Grants and Partnerships Program, Phase II, Cooperative Agreements (NIAID)—promote joint ventures between NIH and both domestic and global entities to facilitate rapid biomedical or biotechnology R&D for infectious diseases to benefit public health; projects should have a commercial potential that could not have been attained without matching funds.

### Interagency and Intra-Agency Agreements

**Y01** NIH Interagency Agreement—provides a written reimbursable agreement by which a component of NIH provides a source of funds to another Federal organization outside the Department of Health and Human Services (DHHS) to acquire specific products, services, or studies.

**Y02** NIH Intra-agency Agreement—provides a written reimbursable agreement by which a component of NIH provides funds to another NIH component or to another organization within DHHS to acquire specific products, services, or studies.

## ACRONYMS

AACTG	Adult AIDS Clinical Trials Group
ACE	Autoimmunity Center of Excellence
ACTG	AIDS Clinical Trials Group
ADCC	Autoimmune Diseases Coordinating Committee
ADV	adenoviral
AIDS	acquired immunodeficiency syndrome
ARAC	AIDS Research Advisory Committee
AREA	Academic Research Enhancement Award
ART	antiretroviral therapy
ASIR	Richard M. Asofsky Scholars In Research award
AVRWG	AIDS Vaccine Research Working Group
BFMB	Budget and Financial Management Branch
BSC	Board of Scientific Counselors
BSE	bovine spongiform encephalopathy
BSIP	Bioinformatics and Scientific IT Program
BSL	biosafety level
CAB	community advisory board
CASG	Collaborative Antiviral Study Group
CAVE	Capital Area Vaccine Effort
CBO	community-based organization
CCTPT	Cooperative Clinical Trials in Pediatric Transplantation
CDA	Confidential Disclosure Agreements
CDC	U.S. Centers for Disease Control and Prevention
CEG	Community Education Group
CEOPP	Community Education and Outreach Partnership Program
CFAR	Centers for AIDS Research
CHAVI	Center for HIV/AIDS Vaccine Immunology
CIPRA	Comprehensive International Program of Research on AIDS
CJD	Creutzfeldt-Jakob disease
CMP	Contract Management Program
CMV	cytomegalovirus
CoV	corona virus
CPCRA	Community Programs for Clinical Research on AIDS
CRADA	Cooperative Research And Development Agreement
CRC	Cooperative Research Centers
CRCA	Clinical Research Curriculum Award
CTA	Clinical Trial Agreement

CWD	chronic wasting disease
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAIT	Division of Allergy, Immunology, and Transplantation
DC	dendritic cell
DEA	Division of Extramural Activities
DHHS	Department of Health and Human Services
DIR	Division of Intramural Research
DMID	Division of Microbiology and Infectious Diseases
DoD	Department of Defense
DTPA	diethylenetriaminepentaacetate
EAMB	Extramural Administrative Management Branch
EIR	Employee Invention Reports
ELISPOT	enzyme-linked immunospot
EM	erythema migrans
EP	electroporation
ESB	Extramural Services Branch
ESPRIT	Evaluation of Subcutaneous Proleukin in a Randomized Intervention
FDA	U.S. Food and Drug Administration
GALT	gut-associated lymphoid tissue
GAS	Group A streptococci
GBS	Group B streptococci
GMB	Grants Management Branch
HAART	highly active antiretroviral therapy
HALT-C	hepatitis C antiviral long-term treatment against cirrhosis
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HOPE	Health Omnibus Programs Extension of 1988 (legislation)
HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
HVAD	HIV Vaccine Awareness Day
HVCC	HIV Vaccine Communications Campaign
HVDDT	HIV Vaccine Design and Development Teams
HVTN	HIV Vaccine Trials Network
IAMB	Intramural Administrative Management Branch
ICER	International Centers for Excellence in Research

ICIDR	International Collaborations in Infectious Diseases Research
ICU	intensive care unit
IHWG	International Histocompatibility Working Group
IL-2	interleukin-2
IL-4	interleukin-4
IND	investigational new drug
INRO	Intramural NIAID Research Opportunities
IOD	Immediate Office of the Director
IOM	Institute of Medicine
IPCP-HTM	Integrated Preclinical/Clinical Program for HIV Topical Microbicides
IPM	International Partnership for Microbicides
IRES	internal ribosome entry site
IRID	International Research in Infectious Diseases
IRTA	Intramural Research Training Awards
ISB	Intramural Services Branch
ITN	Immune Tolerance Network
KMO	Knowledge Management Office
LACMB	Legislative Affairs and Correspondence Management Branch
<i>M.tb</i>	<i>Mycobacterium tuberculosis</i>
MACS	Multicenter AIDS Cohort Study
MADGC	Multiple Autoimmune Disease Genetics Consortium
MSB	Management Services Branch
M-CRADA	Materials-CRADA
MDDT	Microbicide Design and Development Team
MDR-TB	multidrug-resistant tuberculosis
MERIT	Method to Extend Research in Time award
MHC	major histocompatibility complex
MIP	Microbicide Innovation Program
MPIB	Mission Planning and Integration Branch
MR4	Malaria Research and Reference Reagent Resource Center
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MS	multiple sclerosis
MSM	men who have sex with men
MTA	Material Transfer Agreement
MTCT	mother-to-child transmission
MVA	modified vaccinia Ankara
MVDB	Malaria Vaccine Development Branch

NAAIDC	National Advisory Allergy and Infectious Diseases Council
NARAC	North American Rheumatoid Arthritis Consortium
NARSA	Network on Antimicrobial Resistance in <i>Staphylococcus aureus</i>
NDRI	National Disease Research Interchange
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NP	nucleoprotein
NPIB	News and Public Information Branch
NRSA	National Research Service Award
NVITAL	NIAID Vaccine Immune T-cell and Antibody Laboratory
NVP	nevirapine
NVPO	National Vaccine Program Office
OAS	Office of Administrative Services
OBR	Office of Biodefense Research
OCGR	Office of Communications and Government Relations
OCIO	Office of the Chief Information Officer
OCPL	Office of Communications and Public Liaison
OCTANE	Optimal Combined Therapy after NVP Exposure study
OD	Office of the Director
OE	Office of Ethics
OGR	Office of Global Research
OI	opportunistic infection
OMO	Office of Management and Operations
OSPFM	Office of Strategic Planning and Financial Management
OSPRT	Office of Special Populations and Research Training
OSRD	Office of Scientific Resource Development
OTD	Office of Technology Development
OTIS	Office of Technology Information Systems
OTSEP	Office of Training and Special Emphasis Programs
OTT	Office of Technology Transfer (NIH)
OWER	Office of Workforce Effectiveness and Resources
PACTG	Pediatric AIDS Clinical Trials Group
PATH	Program for Appropriate Technology in Health
PAVE	Partnership for AIDS Vaccine Evaluation
PCR	polymerase chain reaction
pDNA	plasmid DNA
PEG-IFN	pegylated-interferon

PEPFAR	President's Emergency Program for AIDS Relief
PFGRCC	Pathogen Functional Genomics Resource Center
PGA	poly-gamma-DL-glutamic acid
PHACS	Pediatric HIV/AIDS Cohort Study
PIDR	Primary Immunodeficiency Diseases Registry
PRMB	Policy and Resources Management Branch
PRP	polyribosylribose phosphate
PRSP	penicillin-resistant <i>Streptococcus pneumoniae</i>
R&D	Research and Development
rAd	recombinant adenoviral vector
RBL	Regional Biocontainment Laboratory
RCA	Research Collaboration Agreement
RCE	Regional Center of Excellence
RCMI	Research Center in Minority Institution
RFA	request for application
RFP	request for proposals
RML	Rocky Mountain Laboratories
rPA	recombinant protective antigen
RPAB	Referral and Program Analysis Branch
RSV	respiratory syncytial virus
SAISB	Scientific Applications and Information Systems Branch
SARS	severe acute respiratory syndrome
SBIR	Small Business Innovation Research
SHIV	simian-human immunodeficiency virus
SIV	simian immunodeficiency disease
SMART	Strategies for Management of Anti-Retroviral Therapy study
SPEB	Strategic Planning and Evaluation Branch
STD	sexually transmitted disease
STI	sexually transmitted infection
STTR	Small Business Technology Transfer Research
TAACF	Tuberculosis Antimicrobial Acquisition and Coordinating Facility
TACC/DACC	Tri-Service AIDS Clinical Consortium Data Analysis and Coordinating Center
TB	tuberculosis
TBRU	Tuberculosis Research Unit
TDRU	Tropical Diseases Research Unit
TEAC	Technology Evaluation Advisory Committee
TIGR	The Institute for Genomic Research
TMP-SMX	trimethoprim-sulfamethoxazole

TMRC	Tropical Medicine Research Centers
TRIM	tripartite motif
TSE	transmissible spongiform encephalopathy
USAID	U.S. Agency for International Development
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USAMRMC	U.S. Army's Medical Research and Materiel Command
USMHRP	U.S. Military HIV Research Program
VDRG	Vaccine Developmental Resources Group
VEE	Venezuelan equine encephalitis
VPP	Vaccine Pilot Plant
VRC	Vaccine Research Center
VRE	vancomycin-resistant <i>Enterococcus</i>
VRSA	vancomycin-resistant <i>S. aureus</i>
WHO	World Health Organization
WIHS	Women's Interagency HIV study
WMRB	Workforce Management Resources Branch
WNV	West Nile virus
WRDB	Workforce Retention and Development Branch

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- <sup>a</sup> Current as of April 2006. For locating personnel not listed, the telephone number for general NIH information is (301) 496-4000. Information is available online at [www3.niaid.nih.gov/about/findingpeople](http://www3.niaid.nih.gov/about/findingpeople).
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| 6610            | —6610 Rockledge Drive, Rockville, MD 20892   |
| 6700B           | —6700B Rockledge Drive, Bethesda, MD 20892   |
| Democracy 2     | —Office of Management for New Initiatives, 6707 Democracy Boulevard, Suite 880, Bethesda, MD 20892   |
| FCRDC           | —Frederick Cancer Research and Development Center, Building 550, Fort Detrick, MD 21702              |
| RML             | —Rocky Mountain Laboratories, 903 South Fourth Street, Hamilton, MT 59840-2999                       |
| TWN1            | —Twinbrook I Building, 5640 Fishers Lane, Rockville, MD 20852  |
| TWNII           | —Twinbrook II Building, 12441 Parklawn Drive, Rockville, MD 20852                                    |
| Building 4      | —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892   |
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| Building 15B-1  | —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892   |
| Building 31     | —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892   |
| Building 40/VRC | —Dale and Betty Bumpers Vaccine Research Center, NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892 |
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